

**Assessment of the Impact of Implementation Research on the Visceral
Leishmaniasis (VL) Elimination Efforts in Nepal: the National Perspective**

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Executive Summary

Nepal signed a Memorandum of Understanding (MoU) with Bangladesh and India in 2005 for the elimination of VL from the region. A major factor in the success of the Kala Azar Elimination program has been sustained input of research evidence into policy and practice.

The objective of this review is to conduct an in depth appraisal of VL research along with the assessment of the contribution and impact of implementation research supported by WHO/TDR in support of the elimination initiative in Nepal.

Although a number of partners have provided different levels of support to VL research at different times over several years, the Special Programme for Research and Training in Tropical Diseases (WHO/TDR) stood out in the appraisal for its uninterrupted contribution to research and capacity strengthening. TDR has since 2005 been engaged in VL research in support of the elimination program including in conducting clinical trials. More recently, it has focused on coordinating and financing implementation research (IR) seeking solutions to problems in diagnosis, treatment, vector control and disease surveillance, including active case detection. Key outcomes of TDR-supported IR include the following:

- TDR supported research on diagnostic tools has contributed to implementation of the rK39 rapid diagnostic test (RDT) as a confirmatory test for VL since 2005.
- Based on evidence from a series of TDR and other partner-supported operational research, miltefosine replaced sodium stibogluconate as a first line treatment from 2008 to 2014. Liposomal amphotericin B replaced miltefosine in 2015 as a result of increased failure and relapse rates identified in TDR funded studies on pharmacovigilance of miltefosine. In addition, through a series of TDR supported projects, combination therapy was introduced into Nepal's national treatment protocol in 2014.
- Furthermore, active case detection with standard operating procedures was incorporated in the national VL elimination protocol based on TDR research.
- Through various TDR supported trials on vector control tools, it was shown that integrated vector management with defined insecticidal tools and environmental management should play a leading role in vector control. An M&E toolkit for IRS operation was introduced into the national programme after development and tests through TDR supported studies.

This desk review of the relevant VL publications and documentation of VL elimination strategies as well as feedback from discussions and workshops with policy makers, researchers, VL treating clinicians, entomologists and the programme staff helped identify the research priorities for the

next ten years to achieve and sustain the VL elimination and work towards Zero Transmission (consolidation and maintenance phase). The plan to leverage funds and resources to maintain the elimination goal without risking a reversal of the gains made so far was also identified.

The current and future priority research areas during the consolidation and maintenance phase were identified by this review and through a workshop. The recommended research topics include:

Short term:

- study on VL relapses in newly treated cases;
- identification of parasite resistance against anti VL drugs;
- validation of rK39 in the new foci and analysis of data on HIV-VL co-infection;
- vector identification, monitoring insecticide resistance and vector bionomics in different ecological areas;
- determination of the role of migrant populations in VL transmission through screening at border posts;
- socio behavioural research on the occurrence of VL in new foci and detection rate of VL in new foci after training the local health workers.

Medium term:

- longitudinal observational study of the prevalence of Hemophagocytic Lymphohistiocytosis (HLH) in paediatric VL cases;
- the combination of different diagnostic tests to monitor VL transmission in low incidence areas;
- investigation and longitudinal follow up of VL progression from asymptomatic to symptomatic cases;
- risk assessment in previously non-endemic areas;
- establishment of diagnostic markers at population level to verify VL elimination and Zero Transmission;
- determination of the infection rate in sand flies in new foci and previously endemic areas considering the changing ecology and climate;
- evaluation of the effectiveness of awareness activities in new foci.

Longer term:

- development and validation of non-invasive antigen-based diagnostic tools;
- role of domestic animals in transmission.

This review document has identified important implementation research areas to support programmatic activities to achieve and sustain VL elimination. Additionally, it is also meant to support other South East Asia Member countries in preparing their dossiers for the WHO validation of VL elimination with specific timelines and an advocacy plan. In addition, the report will serve as a resource for other regional foci, and in particular, Eastern African countries, as they work towards VL elimination.

Table of contents

<u>EXECUTIVE SUMMARY</u>	<u>3</u>
<u>BACKGROUND</u>	<u>11</u>
<u>OBJECTIVES</u>	<u>13</u>
<u>METHODOLOGY</u>	<u>14</u>
<u>IMPORTANT RESEARCH FINDINGS</u>	<u>16</u>
DIAGNOSTIC TESTS FOR VL	16
TREATMENT REGIMENS FOR VISCERAL LEISHMANIASIS	20
VL VECTOR CONTROL	30
VL CASE DETECTION AND SURVEILLANCE	35
<u>CAPACITY BUILDING</u>	<u>44</u>
<u>MAJOR POLICY CHANGES FOR VL WITH TIMELINE</u>	<u>44</u>
<u>PRIORITY RESEARCH AREAS FOR VL FOR THE NEXT TEN YEARS (CONSOLIDATION AND MAINTENANCE PHASE)</u>	<u>51</u>
<u>PLAN FOR TRANSITIONING TOWARDS SUSTAINABLE INTERNAL RESOURCE LEVERAGING FOR CONTINUED IMPLEMENTATION RESEARCH IN SUPPORT OF ZERO VL</u>	<u>52</u>
<u>CONCLUSION</u>	<u>54</u>
<u>REFERENCES</u>	<u>54</u>
<u>ANNEXES</u>	<u>64</u>
ANNEX 1: LIST OF PARTICIPANTS	64
ANNEX 2: AGENCIES AND INSTITUTIONS CONDUCTING VL RESEARCH SINCE 2000	70
ANNEX 3: VL PUBLICATIONS FROM STUDIES IN NEPAL	71
ANNEX 4: NUMBER OF VL PUBLICATIONS BY YEAR AND CATEGORY	82
ANNEX 5: WHO/TDR SUPPORTED VL IMPLEMENTATION RESEARCH CONDUCTED BY THE INSTITUTE OF MEDICINE, TRIBHUVAN UNIVERSITY	83
ANNEX 6: PHIDREC VL RESEARCH SUPPORTED BY WHO/TDR	86
ANNEX 7: VISCERAL LEISHMANIASIS RESEARCH INSTITUTIONS IN NEPAL	93
ANNEX-8: SOP FOR DIFFERENT ACTIVE CASE DETECTION METHODS	95
ANNEX 9: DATA COLLECTION FORM AFTER THE END OF THE SPRAYING CYCLE AT THE DISTRICT LEVEL	100
ANNEX 10: SANDFLY COLLECTION RECORD SHEET	101
	6

ANNEX 11: BIOASSAY TEST RECORD SHEET	102
ANNEX 12: HOUSEHOLD SCREENING REGISTER	103
ANNEX 13: CAMP ATTENDANCE REGISTER	104
ANNEX 14: CASE REFERRAL FORM	106
ANNEX 15: PATIENT TREATMENT CARD	108

List of Tables

Table 1: Research on diagnostic tests for VL

Table 2: Research on VL treatment drugs

Table 3: Implementation research on VL vector control

Table 4: Implementation research on VL surveillance

Table 5: Major strategic changes in the VL control/elimination program in Nepal

List of Figures

- | | |
|----------|---|
| Figure 1 | Structure of the surveillance system in Nepal before 2015 |
| Figure 2 | Structure of surveillance system in Nepal since 2015 |
| Figure 3 | Trend of VL cases and deaths, 2002-2020 |

List of Abbreviations

ACD	Active Case Detection
ADR	Adverse Drug Reaction
BPKIHS	Bisheswor Prasad Koirala Institute of Health Sciences
DAT	Direct agglutination test
DHO	District health office
DNDi	Drugs for Neglected Diseases initiative
DoH	Department of health
EDCD	Epidemiology and Disease Control Division
EVM	Environmental Vector Management
EWARS	Early Warning and Reporting System
FCHV	Female Community Health Volunteer
HA	Health Assistant
HIV	Human Immunodeficiency Virus
HLH	Hemophagocytic Lymphohistiocytosis
HP	Health Post
ICON	Lambda cyhalothrin
ICT	Immunochromatographic test
iHIMS	Health Management Information System
IRS	Indoor Residual Spray
ITN	Insecticide Treated Net
IVM	Integrated Vector Management
IWP	Insecticidal Wall Painting
KA	Kala-azar
LAmB	Liposomal Amphotericin B
LLIN	Long Lasting Insecticidal Net
MIL	Miltefosine
MoHP	Ministry of Health and Population
NHRC	Nepal Health Research Council
NTD	Neglected Tropical Disease
PCD	Passive Case Detection
PCR	Polymerase Chain Reaction
PHC	Primary Health Care
PKDL	Post Kala-azar Dermal Leishmaniasis
PM	Paromomycin
RDT	Rapid Diagnostic Test
RHD	Regional Health Directorate
RTAG	Regional Technical Advisory Group
SOP	Standard Operation Procedure
SSG	Sodium Stibogluconate
TDR	WHO Special Programme for Research and Training in Tropical Diseases
VBDRTC	Vector Borne Disease Research and Training Centre

Background

Visceral leishmaniasis (VL), also known as Kala-azar (KA), is a fatal parasitic disease if untreated, transmitted by sandflies with anthroponotic characteristics in the Indian sub-continent (confined to the human population only, no animal reservoir) transmission mostly affecting socio-economically deprived populations. Worldwide, an estimated 50,000 to 90,000 new VL cases are occurring annually out of which more than 90% of the cases are from 10 countries including Bangladesh, India and Nepal. Approximately 20% of the VL treated cases develop skin condition known as Post Kala-azar Dermal Leishmaniasis (PKDL). These PKDL cases harbour large amounts of amastigote parasites in the skin lesions and are a source of transmission of VL.

Bangladesh, India and Nepal signed a Memorandum of Understanding (MoU) in 2005 to eliminate VL from the region. Later in 2014, the MoU was extended to include Bhutan and Thailand. The national strategy on VL elimination 2008, 2014 and 2019 provided guidelines for the elimination activities in the country. The current national strategy on VL elimination in Nepal (2019) has adopted the following pillars for VL elimination:

- a) Early diagnosis and complete treatment
- b) Integrated vector management
- c) Effective disease and vector surveillance
- d) Social mobilization and partnerships
- e) Improved programme management
- f) Clinical, implementation and operational research

Since 2005, the Special Programme for Research and Training in Tropical Diseases (WHO/TDR) has coordinated and financed implementation research as well as clinical trials in support of the VL elimination initiative in the Indian Sub-continent among the WHO South East Asia Regional Member Countries. WHO/TDR supported implementation research focussed on the country's strategy on VL elimination. TDR supported studies covered diagnosis and treatment of VL, disease surveillance, vector control and surveillance, social mobilization on case detection and case referral, and behavioural change of the community.

Scientific publications, standard operating procedures (SOPs), policy briefs, monitoring and evaluation (M&E) handbooks and other operational documents were developed in collaboration with WHO and national partners and have largely been adopted by the national authorities. The input, together with findings generated through operational research supported by other development partners in these countries, has shaped the regional technical advisory group (RTAG)'s recommendations and helped advance the VL elimination effort in these countries. Every year, TDR organized a joint meeting of program managers, country researchers and

international experts on VL (from WHO/TDR, WHO/NTD, DNDi and McGill university, among others) to update stakeholders on achievements of the program, to share new research findings, identify next priorities and draft proposals for the next phase of implementation research. Country investigators participated in the development of national and regional strategic plans and programs. RTAG meeting recommendations were translated or incorporated into the strategies for VL elimination in the country.

TDR studies in Nepal led by Prof Dr Anand Ballabh Joshi established the burden of VL, and provided critical evidence in a number of areas including on the health seeking behaviour of the population, cost-effectiveness of interventions, Active Case Detection (ACD), diagnostic and treatment delays, feasibility of new interventions, effective and long lasting vector control interventions, housing as a risk factor for VL transmission, the role of the front line health workers, among others. Based on the findings from mainly these studies in particular, the national VL elimination program developed strategies, guidelines and implementation plans for the attack phase of VL elimination in Nepal. This was complemented by research in Bangladesh and India related to the treatment, diagnosis, vector control and surveillance of VL and PKDL. These studies significantly contributed to the update and development of the national strategic plans, disease control guidelines and in the development of human resources for VL, which eventually led to the 90% reduction of VL incidence to a level below the elimination target.

From 1990 to 2000, there were only three articles published on VL treatment in Nepal, out of which two were TDR funded. In addition to this, there was one TDR funded surveillance study. However between 2001 and 2010, there was an increase in publications from studies conducted in Nepal on VL with four publications on treatment, six on diagnosis and two on surveillance. Intensive research was done on vector control in the same period resulting in a total of eight articles published from Nepal. The number of publications on vector control and surveillance was highest between 2011 and 2020 with thirteen studies published on vector control and eighteen on surveillance. In this same period, the number of studies on treatment and diagnosis was in similar range as in the previous years (Annex 4).

Although significant progress has been made in Nepal with around 90% reduction in VL cases as compared to 2005, to sustain progress towards the elimination goal and, if possible achieve Zero Transmission, more efficient and effective methods for active case detection and vector management which respond to the changing epidemiological profile in the countries are required. A number of challenges related to the sustainability of maintaining the VL incidence below the elimination threshold have yet to be tackled, including disease occurrence in new foci, identification or even prediction of outbreaks, PKDL burden and PKDL treatment outcomes and HIV-VL co-infection. Liposomal amphotericin B (LAmB) is the first line drug for the treatment of

VL; however, its current efficacy has not been determined. The magnitude and epidemiology of HIV-VL co-infection in Nepal has not yet been analysed. Additionally, strategies for integrated services, vector control and prevention of emerging new foci have to be improved. More information is needed in a number of areas such as on the transmission dynamics of the disease, its basic reproduction rate, the rate of relapse after treatment, the role of cutaneous leishmaniasis and on the infection potential of PKDL and asymptomatic infections.

Proper assessment and documentation of the contribution of implementation research to the VL elimination programme, its successes as well as its challenges, is necessary, particularly now after the COVID-19 pandemic, in order to plan future directions as well as to derive lessons for other regional VL foci. Documentation of the regional achievements and lessons learned could serve as reference material for VL programmes in endemic African countries.

Objectives

The objective of this in-depth VL research review was to assess the contribution and impact of implementation research on visceral leishmaniasis (VL) in support of its elimination as a public health problem in Nepal in order to derive lessons for similar elimination efforts in other foci and for other similar diseases. The main aim of the study was to:

- describe key milestones of implementation research in the course of VL elimination in Nepal
- review the implementation research conducted through academic institutions, the government, non-government organizations, and other partners and its impact on national policies and strategies
- document key characteristics of the VL implementation research including agenda, content, trend, support base, process, partnership, and other related aspects (research topics addressed, main findings obtained, source of funding, investigator teams and institutions and capacity built, among others) and to summarize key lessons that could be applied in other regional foci
- review the contribution of TDR supported implementation research to the VL elimination programme
- identify priority research areas for sustaining the VL elimination in Nepal and to develop specific recommendations regarding research funding

Methodology

The following methods were used to develop this document:

- a) *Desk review*: Desk review of relevant VL publications from Nepal, documents on VL elimination, strategies and operational plans of the country or other documents relevant to the country (from internal and external sources). The published articles were accessed through pubmed and google. Mesh terms 'leishmaniasis, visceral' and text words such as 'rK39,' 'miltefosine,' 'amphotericin,' active case detection, surveillance, and 'vector control' with and without restriction to MeSH terms 'Nepal.' We screened each article for eligibility around 5 thematic areas in alignment with the National Strategic Framework for VL Elimination: (1) diagnostic tool; (2) treatment; (3) detect new cases, surveillance; (4) vector control; (5) community participation. Our focus was to include almost all TDR supported studies in Nepal. National Strategic Guideline on Visceral Leishmaniasis Elimination, 2008, 2014 and 2019, Indoor residual spraying guidelines were reviewed. WHO technical reports, expert consultation meeting reports, TDR annual reports, tool kits developed for VL, and Regional Technical Advisory Group meeting reports were also reviewed. Expert commentaries, opinions, and reviews authored or funded by WHO TDR have also been included.
- b) *Expert consultations*: The team consulted national VL programme managers, VL treating clinicians, entomologists and researchers to collect information on operational research activities, alignment with the programme and implementation research needs to achieve sustainability in VL elimination. The consultations included WHO SEARO and the WHO country office. National program officers were engaged since inception and remained on board throughout and aware of the activities.
- c) *Organization of workshop*: A five day workshop was organized on 23 - 27 September, 2021 among academic institutions, national programme managers and development partners. A total of 48 participants attended the workshop. The detailed information of the participants is listed in Annex-1. Due to the ongoing COVID-19 pandemic, the workshop was organized in three separate sessions as follows:
 - o Clinicians, program staff and researchers (26 participants, over two days)
 - o Entomologists, researchers and program staff (19 participants in a one day meeting)
 - o Former directors, development partners, researchers, academics and programme staff (35 participants over two days)

Clinicians: On the first half of the first day, there were presentations from clinicians and program staff. The clinicians invited to the workshop were individuals who had been treating VL cases for the past 3-14 years. These were followed by general discussion and feedback from workshop participants. Breakout discussions were held in two groups where one group addressed

treatment and the other diagnosis. The working group reports and recommendations were presented to the plenary on the following day.

Entomologists: Similarly, the workshop with the entomologists started with presentations by the entomologists and by program officers on the current status of vector control as well as new contributions from VL vector control research. This was followed by discussion and feedback on how to improve the vector control operations.

Programme staff: The last two days of the workshop were for the programme staff actively involved in VL at the policy level. Among the attendees were the director general of DoHS; the director, program manager and staff of EDCD; WHO country representative; former directors; representatives from development partners; academics and the executive chief of NHRC. They presented their perspective on VL elimination, research contribution and future research requirements. The workshop ended with identifying the research and programmatic priorities as well as leveraging resources to achieve and maintain the VL elimination.

Important Research Findings

Diagnostic tests for VL

Early and accurate diagnosis with proper treatment is one of the main pillars in the VL elimination strategy. TDR's research priority has been to develop a diagnostic test that is simple, highly sensitive, specific and reproducible in field settings with a suspicion index lower than that of a referral hospital (Boelaert et al., 2007). Two of the serological tests that are appropriate for field settings and used for the VL elimination program are the direct agglutination test (DAT) and rK39 immunochromatographic test (ICT). DAT was initially used as a diagnostic tool for VL from the early 1990s. WHO/TDR supported assessment of DAT as a diagnostic tool (Joshi et al., 1999) before its field application revealed it to be specific, sensitive and simple enough to be performed in field settings. Although DAT has a similar sensitivity and specificity as that of rK39, the latter is more cost effective and simpler to use in field settings (Bern et al., 2000; Chappuis et al., 2003). Validation studies for rK39 done in Nepal showed more than 95% specificity and sensitivity in different TDR supported studies conducted from late 1990s to the early 2000s (Bern et al., 2000; Chappuis et al. 2003; Boelaert et al. 2004; Das et al., 2007). Although the favourable results of research on rK39 were known since the early 2000s, it was introduced as a diagnostic tool in the national VL elimination program only in 2005. At this time, the test was available at level II and above health institutions in endemic districts. A diagnostic test performed on 87 VL patients in Nepal in 2001 - 2002 showed that rK39 met most of the ASSURED criteria and confirmed that it could be used as a single cost effective confirmatory test (Chappuis et al., 2006). The rK39 test is thus the first line diagnostic tool for VL since 2005.

However, with the rising numbers of VL cases in new foci during the consolidation phase of VL elimination, it is becoming apparent that, in addition to rK39, molecular tests should be explored for their application as alternatives to confirm VL cases. Studies by Deborggraeve et al., 2008 and Shrestha et al., 2019 revealed that molecular tests such as PCR have a high sensitivity and specificity and are more reliable in the presence of HIV co-infections, relapses, PKDL, CL and MCL cases. In addition, molecular tests can also help to better understand the origins and the spread of different VL strains. A multicenter study conducted by Ejazi et al., 2019 revealed that the LAg dipstick test can also be used as an effective confirmatory test for VL. Current VL National guidelines in Nepal recommend the use of PCR to confirm diagnosis in doubtful cases. The parasitological method is also one of the most reliable diagnostic tools for VL detection as it directly demonstrates the amastigote form of the parasite in the organ (Srividya et al., 2011). Unfortunately, the test is not appropriate for field settings because of its low sensitivity. Nevertheless, the service is available at level III (tertiary hospital and referral centers). According

to the national guideline, a parasitological test is required in specific clinical situations such as in the case of treatment failure, in coinfections, PKDL or in drug resistance.

By definition, confirmed VL cases have had fever for at least 2 weeks; however, it could be beneficial to perform rK39 tests on patients with a fever history of 5 days to detect cases at an early stage. Training of village health workers could facilitate the access to rapid diagnosis by spreading important messages and alerting people with fever, hence shortening the delay in the diagnosis. With the occurrence of VL in new foci, the availability of diagnostic tools in these areas is important. Although rK39 has a high sensitivity and specificity, different Ag based tests should be further explored and validated. As the number of cases are low, the specificity of any new test must be very high, likely over 95% to be useful. Additionally, due to the changing presentation of VL, further research on the sensitivity and specificity of rK39 in new foci should be considered. Standardization of RDT is required to prevent sub-standard products. In addition, higher and more specific DAT cut-off titres should be investigated in order to differentiate between zero and low transmission. Combining the Leishmanin skin test and DAT or rK39 could help in assessing the transmission potential in a community. Likewise, molecular studies with PCR should be conducted to understand the origin and the spread of different strains. Diagnostic markers at population level, which include asymptomatic infection, progression to PKDL and VL-HIV co infected patients, are required to maintain the VL elimination. Although these could be the research opportunities in diagnostic aspects of VL, it is better to use the available resources on strengthening surveillance using existing technologies as opposed to developing new technologies.

Table 1: Research on diagnostic tests for VL

Author Year	Year Donor Engagement	Study Design Subjects Sample Size	Results	Conclusion
Joshi et al., 1999	UNDP/World Bank/WHO	Diagnostic evaluation of DAT before its field application. 15 VL patients	VL cases reactive to anti-leishmanial antibody at >1:3200. Sens- 100%; Spec- 99.2% PPV: 100%; NPV: 99.2%	DAT is simple, rapid, reliable, economic, safe and adaptable to micro-techniques using micro titer plates. It is simple enough to be used in a field laboratory.
Bern et al., 2000	1999	Diagnostic evaluation (rK39 and DAT) study	rK39 dipstick test Sens- 100% Spec- 100%	rK39 is more advantageous, simple to perform and

		92 VL patients	DAT Sens- 100% Spec- 93%	interpret in the field setting.
Chappuis et al., 2003	1999-2000 TDR Funding	Diagnostic evaluation (rK39 ICT, DAT) study 184 VL patients	rK39 ICT sens- 97%, spec-71%; DAT sens-99%, spec-82%;	rK39 ICT equates well with DAT and is easy to use in field settings. rK39 can be used as a diagnostic tool for screening and confirmatory tests for VL but only in high prevalence VL areas.
Boelaert et al., 2004	2000-2002 TDR Authorship	Diagnostic (rK39 ICT, FGT, IFAT, DAT) evaluation study 310 VL patients	rK39 ICT sens- 87.4%, spec-93.1%; FGT sens-39.9%; IFAT sens-28.4%; DAT sens-95.1%	DAT and rK39 ICT can replace VL diagnosis via bone marrow or splenic aspiration for the treatment decision in the VL elimination program.
Chappuis et al., 2006	2001-2002 TDR Funding and Authorship	Diagnostic (rK39 ICT, FGT, KAtex) evaluation study 85 VL patients	rK39 ICT sens-89%, spec-90%; FGT sens-52%; KAtex sens-57%; Reproducibility higher for rK39 ICT (k=0.87) compared to FGT and KAtex;	rK39 meets most of the criteria of ASSURED.
Das et al., 2007	1998-2000	Evaluation of diagnostic tool for PKDL 35 VL patient	DAT Sens- 100% Spec- 93% rK39 Sens- 96% Spec- 100%	rK39 is cost effective, easy to use and store in field condition comparatively.
Boelaert et al., 2007	Authorship	Review of considerations for evaluation of diagnostic tests (test for case detection, cure, relapse, surveillance, drug	Lower spec (71%) in Nepal in early prototype; higher spec in later generation of InBios ICT and DiaMed ICT	Standardized methodology for the evaluation of RDT is required to prevent the substandardization of product being used.

		resistance, certification of elimination)		
Boelaert et al., 2008	2003-2006 TDR Funding and Authorship	Diagnostic (rK39 ICT, DAT-FD, KAtex) evaluation study 1, 150 VL patients	DAT-FD: Sens- 98.5%; Spec- 95.4%. rK39: Sens- 96.5%; Spec- 90.9%. Katex: Sens- 35.8%; Spec- 97.8%	DAT-FD, rK39 ICT recommended.
Deborggraeve et al., 2008	2000-2002 European Communities	Diagnostic accuracy of PCR, 173 VL patients	Sens- 92.1% in blood, 92.9% in bone marrow Spec- 99.64%	High sensitivity and specificity but should be used with standardized clinical VL case definition. Comparatively more reliable in HIV co- infected VL patients as well as for the follow up.
Boettcher et al., 2014	2013 Institute of Tropical Medicine, Antwerp	Review of accuracy of rapid diagnostic test	rK39 ICT sens-97%, spec-90.2%; Latex agglutination test sens-50.8%, spec-95.3%	rK39 ICT recommended in patients with febrile splenomegaly and no past VL history.
Singh and Sundar, 2015	2015 National Institute of Allergy and Infectious Disease, National Institute of Health	Review of current diagnostic test	rK39 showed high diagnostic accuracy. DAT showed satisfactory results.	Standardized clinical case definition should also be used while making diagnosis for VL.
Ejazi et al., 2019	2019	Diagnostic (LAg dipstick test) evaluation study, 98 VL patients	Sens- 100% Spec- 93.33%	It can be single cost effective confirmatory test for VL.

Shrestha et al., 2019	October 2015 - December 2016 Nepal Academy of Science and Technology	Confirmation of Leishmania species via molecular approach in VL suspected patients from non-program districts. 6 suspected VL patients	PCR: Positive- 2 Negative- 4. 2 positive PCR were also positive for bone marrow aspiration.	Innovative strategies like molecular tests should also be incorporated for better understanding of the origin and spread of these strains. Subsequent government plan and action is required to be included in new foci areas as well.
Cloots et al., 2020	October-December 2016 The Directorate-General for Development Cooperation of Belgium	Assessment of DAT as a marker of infection for future surveillance. 6609 participants	DAT prevalence for children <10 years: (2006)- 4.1%, (2016)- 0.5%; Adjusted risk ratio for seropositive: 0.44 for 2016, 0.04 in children <10 years	DAT could be a useful tool for monitoring the transmission of <i>L. donovani</i> , however a higher and more specific DAT cutoff titre is required to accurately differentiate between zero and low transmission.

Treatment regimens for visceral leishmaniasis

The objective of VL treatment is to cure the patient while minimizing the side effects and toxicities of the drug, preventing the complications, supporting the nutritional status of the patient as well as managing other medical conditions, and reducing the risk of relapse and of PKDL. The outcomes of the treatment are directly related to the overall management of VL patients and does not depend solely on anti kala-azar drugs. SSG was first introduced in Nepal as early as in 1982 and has served as a first line treatment drug from 1994 onwards. The study conducted by Karki et al., 1998 on 54 VL patients with SSG revealed a satisfactory result with the efficacy being relatively better in those treated for a longer period. However, by 2001, SSG had shown increasing failure rates of 10 to 30% in Nepal (Rijal 2003) and 60% in Bihar (Sundar 2000). Although the failure rates were relatively lower in Nepal, the increase in failure rates in neighbouring Bihar posed a significant threat. The studies done by Rijal et al., 2003 and 2009 revealed that those patients living near the Bihar border had resistant parasite strains urging the need for an alternative treatment. Amphotericin B was introduced for the treatment of VL

in 1994. TDR supported the phase IV trial of miltefosine (MIL) conducted by Bhattacharya et al., 2007 which revealed that it was a safe and effective oral drug for VL treatment. In 2008, oral monotherapy of miltefosine was introduced until 2014 as a first line drug for VL treatment in case of no contraindication. TDR supported the phase IV trial conducted by Banjara et al. 2012 in Saptari district; the study was conducted after the introduction of miltefosine as a first line regimen. Although MIL was relatively safer and better than SSG, it is teratogenic and hence contraindicated in pregnancy and lactating mothers. In addition, women in reproductive age are required to take contraceptives while being treated with MIL and pregnancy is not recommended for 5 months post treatment with MIL. Furthermore, the study by Rijal et al., 2013, reported 10-20% of relapse after the treatment with MIL. In addition, Banjara et al., 2012 and Uranw et al., 2013 in their studies cautioned that poor adherence and insufficient dose were associated with the occurrence of relapse. On average, one day of not taking MIL led to an 1.08 fold increased odds of treatment failure (Dorlo et al., 2014).

Amphotericin B, a systemic antifungal agent, has been in the treatment protocol for VL since 1994 and was recommended as second line treatment from 2010 onwards even though it had poor pharmacovigilance and required slow intravenous infusion. On the other hand, the liposomal formulation of amphotericin B was safer requiring short course treatment without affecting the efficacy of the therapy. The TDR supported dose finding studies conducted in India revealed that L-AmB was safe, effective and favourable for the treatment of VL with minimal toxicity (Thakur et al., 1996; Sundar et al., 2003), although a substantial reduction in price was necessary to enhance its deployment (Sundar et al., 2004). In May 2007, WHO signed an agreement with Gilead to produce AmBisome for a no-profit-no-loss price for the treatment of VL in developing countries (Boer et al., 2011). Sinha et al., 2010 and Sundar et al., 2010 in their studies reported that single infusion L-AmB was safe, effective and not inferior to the conventional therapy. Furthermore, when combined with other drugs, the chances of developing parasite resistance were reduced. In 2014, L-AmB was introduced in the treatment protocol for VL and it is since 2015 the first line treatment in the national guideline for VL elimination.

TDR supported trials conducted in the Indian subcontinent showed that combined therapies were more favourable in comparison to monotherapy (Thakur et al., 1995; Thakur et al., 2000; Sundar et al., 2010). These studies revealed that combined therapy reduces the dose requirements without risking the cure rate. RTAG recommended the use of combined therapy for the consolidation phase. The national treatment protocol, introduced in 2014, combined the therapy as a second line of treatment for VL. The combination regimen consists of Liposomal Amphotericin B (L-AmB) (5mg/kg, single infusion) plus 7 days MIL (50mg BID) or alternatively L-AmB (5mg/kg, single infusion) plus 10 days Paromomycin (PM) (11mg/kg base) or MIL plus PM

for 10 days. Combined therapy has replaced Amphotericin B to second line treatment shifting it to third line treatment in the national guideline in 2019.

Paromomycin, an aminoglycoside drug with anti-Leishmaniasis properties, is another anti kala-azar drug introduced as combination therapy in 2014 and as a fourth line therapy as per national guidelines 2019. Although TDR initiated the clinical trial of Paramomycin to replace SSG (Jha et al., 1998), its development has been slow and was eventually halted as the focus was put on miltefosine. However, paramomycin trials conducted by One World Health have since supported its registration (Sundar et al., 2007 and Sinha et al., 2010).

Pharmacovigilance

Pharmacovigilance is the science and activity in relation to detection, assessment, understanding and prevention of adverse effects or any other possible medicine-related problems (WHO, 2002). Pharmacovigilance deals with the assessment of the therapeutic benefit as well as the adverse effect of drugs. Various factors like disease burden, status of healthcare delivery in public and private sectors, current status of the pharmacovigilance programmes and assessment of risk and effectiveness of the drug should be considered before designing the pharmacovigilance activity. In recent years, to combat public health diseases, donor-funded programmes have been set in motion. Although public health programs offer ample benefits, there is also a possibility of harm at large scale as many of these programmes are involved in the administration of drugs and vaccines, some of which are new and some can be relatively unsafe. Therefore pharmacovigilance plays a major role, as its core purpose is to ensure patient safety, evidence-based information on medicine safety along with providing reliable and balanced information on the risk-benefit profile of the drug.

In Nepal, the VL elimination program in 2014 introduced a VL focused pharmacovigilance program with the combined effort of EDCCD, DoH, MoHP and BPKIHS supported by PATH India. The drugs recommended for the treatment of VL have side effects which can affect the quality of life as well as the compliance to the treatment. For example, Miltefosine monotherapy is no longer recommended for VL treatment due to its reduced efficacy and longer treatment duration as well as side effects such as diarrhoea and vomiting but is still the first line treatment for PKDL. Therefore, continued monitoring while using anti VL drugs is necessary to document side effects. Good pharmacovigilance is an important part of the VL elimination program as it ensures the safety of the cases under treatment. Nurses, doctors and paramedics treating and monitoring VL patients play a major role in the detection and documentation of adverse drug reactions (ADRs). They are required to fill an “adverse event reporting form” if they suspect the possibility of occurrence of a potential ADR events with the signature of the physician treating the case. Those forms should be submitted to the nodal contact person at respective monitoring

sites and sent to the EDCD from those sites. The national guideline for the VL elimination program recommends monitoring of side effects through laboratory tests like haematological tests, liver function tests, kidney function tests, electrolytes and ECG wherever available. Information received on major or minor side effects through these tests should be further reported to the local health institution (Annex 15).

Monitoring the prescribing practice, health care provider's knowledge, availability of the drugs as well as its quality and the safety should be consistent. Furthermore, quality assurance of the drugs and its storage should be monitored. Along with this, there should be re-evaluation of the pharmacovigilance of the VL drugs currently used in the treatment. Similarly, the follow up of the treated cases should be monitored strictly. In addition to this, the follow up after treatment of VL should be further increased in order to have a better understanding of the relapse cases. Retrospective analysis of the treatment pattern in the relapse and treatment failure cases is recommended. Further research for safer drugs should also be done along with the development of alternative drugs or treatment schemes for PKDL.

Table 2: Research on VL treatment (drugs)

Drug	Author Year	Year Donor Engagement	Study Design Subjects Sample Size	Result	Conclusion
Sodium Stibogluconate (SSG)	Karki et al., 1998	1994-1997	Evaluation of SSG efficacy at a dose of 20mg/kg/day for 20 days and 30 days. 54 VL patients.	For 20 days efficacy - 77.78% For 30 days efficacy - 92.59%	Longer period (30 days) treatment is more effective with higher cure rate and minimum side effects.
Sodium Stibogluconate (SSG)	Rijal et al., 2003	July 1999- August 2001	Evaluation of SSG efficacy at a dose of 20mg/kg/day for 30 days 110 VL patients	Cure - 90% Failure - 10%	SSG efficacy is satisfactory except for those living near antimony resistant VL areas of India. Thus suggesting there has been spread of resistant strains in Nepal, requiring policy to control further spread.
Sodium Stiboglucon	Rijal et al., 2009	January 2001 -	Evaluating the risk factors for	Cure - 90.5% Failure - 9.5%	Cure rate, comparing from the view of intention-to-

ate (SSG)		September 2003 European Commission Community Research	the therapeutic failure of SSG at a dose of 20mg/kg/day for 30 days 169 VL patients		treat is much lower (77.3%). Risk factors for treatment failure were prolonged fever, interruption in treatment, living close to Bihar high resistance area and ambulatory care.
Miltefosine (MIL)	Bhattacharya et al., 2007	TDR funded	Evaluation of the feasibility of treatment of VL patients with MIL in field setting. 1132 VL patients.	95.5% compliance for 28 days treatment; 85.8% returned after 6 months after treatment for follow up; 82% cure in intention to treat analysis and 95% by per protocol analysis.	Oral miltefosine is safe and effective for the treatment of VL in an outpatient setting in a VL endemic area. However due to its teratogenicity, it should be avoided in pregnancy.
Miltefosine (MIL)	Banjara et al., 2012	2009 - 2010 TDR funded	Evaluation of clinical management of VL after intervention within the context of the National VL elimination program. 28 VL patients	No significant change in healthcare facilities. Use of MIL was the same as amphotericin B. Well aware about the side effects of MIL. Home based treatment for MIL was approved.	Counselling by a physician requires further strengthening. Availability of drugs plays a significant role in prescription behaviour.
Miltefosine (MIL)	Uranw et al., 2013	March 2010- August 2011	Evaluation of adherence to MIL 171 VL patients	Adherence- 83%; more was seen in patients who	Poor adherence was associated with relapse. Effective counselling, understanding of side

		Belgian Federal Cooperation (ITM-DGD framework agreement)		were literate and aware of the side effects.	effects, action of MIL along with home visit can prevent poor adherence.
Miltefosine (MIL)	Rijal et al., 2013	Oct 2008-April 2011 European Commission's seventh Framework Program	Evaluation of Miltefosine clinical outcome upto 12 months after therapy 120 VL patients	Cure - 95.8% Relapse at 6 months - 10.8% Relapse at 12 months - 20%	Effectiveness of MIL has reduced with increasing relapse, thus requiring better therapeutic options for VL elimination.
Miltefosine (MIL)	Dorlo et al., 2014	March 2010-August 2011	Evaluate the relationship between MIL drug exposure and treatment failure with VL. 81 VL patients	1 day decrease in miltefosine exposure led to 1.08 fold increased odds of treatment failure. Children (<12 yrs) are risk factors for treatment failure.	Sufficient dose of MIL is required to achieve successful VL treatment. MIL treatment guidelines for adults and children are the same which needs to be re-evaluated.
Liposomal Amphotericin B (L-AmB)	Thakur et al., 1996	TDR	Evaluation of 3 regimens of liposomal amphotericin B (total doses: 14mg/kg, 10mg/kg and 6mg/kg) for VL treatment. 30 VL patients	Clinically cured in all patients by 24 th day. Hb, WBC, serum albumin and body weight improved by 24 th day and was normal by	Liposomal amphotericin B is safe and highly efficacious for VL treatment with minimal side effects and toxicity.

				180 th day. No relapse within 12 months follow-up.	
Liposomal Amphotericin B (L-AmB)	Sundar et al., 2003	Gilead Science	Evaluation of Single dose L-AmB (7.5mg/kg) in India. 203 VL patients	Cure- 90% Failure- 10%	Single dose L-AmB treatment is safe and effective and can be used for mass treatment of VL.
Liposomal Amphotericin B (L-AmB) and Amphotericin B	Sundar et al., 2004	May – July 2001 TDR; The Liposomal Company; Sitaram Memorial Trust	Evaluation of efficacy of L-AmB (2mg/kg for 5days) vs Amphotericin B (1mg/kg on alternate days for 30 days). 153 VL patients	Final cure rates were similar in both treatment. Estimated cost for 25 kg patients: USD 872 for L-AmB; USD 417 for amphotericin B	Liposomal amphotericin B is safe as well as better tolerated. Its short course also shortens inpatient stay. Substantial reduction in the price of liposomal amphotericin can enhance its deployment.
Liposomal Amphotericin B (L-AmB)	Sinha et al., 2010	July 2007- May 2008 The Medecins Sans Frontieres Visceral Leishmaniasis Treatment Program, Medecins Sans Frontieres Operational Center	Evaluation of L-AmB's effectiveness and Safety at the dose of 20mg/kg	Intention-to-treat - 98.8%; per protocol - 99.6%; Intention-to-treat worse-case scenario - 81.3%	Safe and effective but reduced dose and combination with partner drugs can also be effective. This also reduces the chances of parasite resistance. Lowering the cost of L-AmB is recommended.
Liposomal Amphotericin	Sundar et al.,	February 2008 -	Evaluation of single dose L-	Cure at 1 month:	Single infusion L-AmB is not inferior to conventional

n B (L-AmB) and Amphotericin B	2010	March 2009	AmB in comparison conventional amphotericinB deoxycholate 412 VL patients	L-AmB therapy-100%, Conventional therapy-98%; Cure at 6 months: L-AmB therapy-95.7% Conventional therapy-96.3%	therapy and is also less expensive comparatively.
Paromomycin (PM)	Jha et al., 1998	June 1993 - August 1995 UNDP/World Bank/TDR	Evaluation of Paromomycin's efficacy and tolerability in comparison to SSG 120 VL patients	Cure for Paromomycin at: 12mg/kg/day - 77% ; 16mg/kg/day - 93% ; 20mg/kg/day - 97% ; Cure for SSG- 63%	A 21 day course of Paromomycin at the dose of 16 or 20mg/kg/day can replace SSG as a first line of treatment.
Paromomycin (PM)	Sundar et al., 2007	June 2003 - November 2004 OneWorld Health; TDR/WHO	Evaluation safety and efficacy of Paromomycin in comparison to amphotericin B 667 VL patients.	Final cure rate at 30 days: Paromomycin (502 patients at 11mg/kg): 94.6%; Amphotericin B(165 patients at 1mg/kg): 98.8%	Paromomycin is safe and efficacious and non-inferior to amphotericin B.
Paromomycin (PM)	Sinha et al., 2011	One World Health	Evaluation of Paromomycin's safety and efficacy in outpatient settings. 494 Intent to Treat Population;	Dose:11mg/kg Initial Cure at 21 days: 99.6%; Final Cure after 6 months: 94.2%; Adverse	Paromomycin is safe and efficacious to use in an outpatient setting.

			479 Efficacy Evaluation Population	Effect- 5%;	
Combined Therapy (PM + SSG)	Thakur et al., 1995	UNDP/World Bank/WHO TDR	Evaluation of safety and efficacy of PM (12 or 6mg/kg/d) and SSG (20mg/kg/d) for 20 days as a combined therapy.	Cure: (PM12mg/kg/d+SSG 20mg/kg/d): 88%; (PM6mg/kg/d +SSG 20mg/kg/d): 69%	Combined therapy with PM at 12mg/kg/day for 20 days is more effective and can be considered as a safe replacement for SSG alone for 40 days.
Combined Therapy (PM + SSG)	Thakur et al., 2000	1996 UNDP/World Bank/WHO/TDR	Evaluation of the safety and efficacy of PM (12 or 18 mg/kg/day) plus SSG (20mg/kg/day) for 21 days compared to only SSG (20mg/kg/day) for 30 days in VL treatment. 150 VL patients	Final Cure: PM 12 + SSG: 92.3%; PM 18 + SSG: 93.8% SSG alone: 53.1%	Combined dose of PM at 12 or 18mg/kg with standard dose for SSG for 21 days was more effective than SSG alone.
Combined Therapy (L-AmB + MIL)	Sundar et al., 2010	TDR	Evaluation of safety and efficacy of L-AmB (5mg/kg) plus MIL (2.5mg/kg/day for 14 days). 135 VL patient.	Intend to Treat cure rate at 6 months: 91.9%; Per protocol cure rate: 97.6% (124 of 127 evaluable patients). Side effects were fever, rigors and back pain	Combination therapy has good efficacy, tolerance and feasibility of administration without compromising the cure rate.

				due to L-AmB; gastrointestinal side effects by MIL.	
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VL vector control

Integrated vector management (IVM) is a rationale in the decision-making process for the optimal use of resources with organised structures for vector control. Joshi et al., 2008 and Joshi et al., 2009 in their TDR funded study found that IVM can play a vital role in the elimination program. Introduced in the 2010 national guidelines for VL elimination, IVM emphasizes the participation of communities to warrant sustainability. VL prevention through vector control is one of the major strategies of the elimination program. TDR funded studies have found that IRS, ITN and insecticidal wall painting (IWP) are effective ways to control sand flies in Nepal (Banjara et al., 2019). IRS with DDT, Malathion and Lambda cyhalothrin (ICON) was used from 1992 until 2002. TDR funded studies done from 1991 to 2001 revealed that the disease incidence before and after the insecticide spray was similar due to the resistance developed as a result of poor insecticide management (Joshi et al., 2003). Hence from 2003 on, the rotational substitution of synthetic pyrethroids was introduced in order to avoid vector resistance. Alpha cypermethrin was used in 2003 and 2012 while Lambda cyhalothrin (ICON) was reintroduced in 2007. A Lambda cyhalothrin study funded by TDR exhibited 97% of mortality and a beneficial impact of IRS for up to 4 weeks after the insecticide spraying (Chowdhury et al., 2010). However, the substandard performance and management of the spraying activity increased the risk of insecticide resistance (Diwakar et al., 2010). The studies on the protective efficacy of LLINs showed contradictory results in some cases. While the studies by Joshi et al., 2009 and Picado et al., 2010 did not show a significant reduction of VL incidence after the use of LLINs, the study by Das et al., 2009 found LLINs to be a favourable alternative for IRS. LLIN distribution started in 2009 as per the national guidelines for VL elimination. The studies on combined vector management interventions in Nepal, funded by TDR, showed favourable outcomes and a benefit for the elimination program (Joshi et al., 2009; Das et al., 2009; Banjara et al., 2019). Studies by Joshi et al., 2009 and Das et al., 2009 also suggested that integrating environmental management (EVM) with other vector control methods can be highly beneficial for the VL elimination program. Furthermore, the TDR funded studies by Huda et al., 2016 and Banjara et al., 2019 revealed that durable wall lining together with EVM, can be an alternative for a long term vector control strategy.

Vector control in current Nepal's national VL elimination programme mostly relies on indoor residual spraying (IRS) using pyrethroids. IRS is done in VL case reported villages for three years in two cycles a year (April-May in the first cycle and September-October in the second cycle). The domestic budget is used for IRS. The new vector control tools such as insecticidal wall paint with promising results could be complementary to IRS for VL vector control. Combining IVM with different models of active case detection could be beneficial for the elimination of the VL.

Providing proper quality training for the sprayers will be crucial for reducing the chances of vector resistance. Additionally, checking the quality of the spraying procedure can prevent vector resistance. Moreover, routine baseline susceptibility testing will be important for maintaining the efficacy of the available insecticides. Also, IRS project refinement, adaptation to the biting behaviour of the vector as well as to the unstable transmission pattern as a result of changing ecologies should be addressed.

During the consolidation and maintenance phase, with the emerging new foci, vector identification and vector surveillance should also be emphasized to sustain the VL elimination. Additionally, research on EVM, LLINs, insecticide resistance and vector bionomics should be advanced. Beside this, the continuation of educational and awareness programs on EVM and LLINs to prevent VL should be encouraged. These programs should also be included in areas of new foci. Implementation of the principles of IVM should be applied as it will help to sustain the VL elimination.

Table 3: Implementation research on VL vector control

Interven tion	Author Year	Year Donor Engagement	Study Design Sample Size	Result	Conclusion
IRS	Joshi et al., 2003	1991-2001 WHO/TDR	Analyse the effectiveness of the IRS. 21 VDC	Disease incidence was found to be same before and after insecticide spray	The resistance was developed due to haphazard use of insecticides without proper research, lack of skilled manpower and community participation.
IRS , LLIN, EVM	Joshi et al., 2009	WHO/TDR	Evaluate the efficacy of different intervention VL vector management. Alpha-cypermethrin e was used in IRS. PermaNet	IRS showed significant reduction in sand fly densities. LLINs didn't have a significant negative effect on the density of sandflies.	Vector control provides support to the VL elimination program. IRS requires strengthening appropriate quality with trained technical support provides efficacious results in vector

			nets were used for LLINs. Lime/mud mixture was used for wall plastering. 2 Districts, 24 cluster from each districts.	EVM using lime plastering had significant sand fly density but at only one site.	control. Further research is necessary on LLINs. EVM's non-significant result in one site could be due to compromise in the quality of lime product.
IRS, LLIN, EVM	Das et al., 2009	November 2006 - April 2007 TDR	Comparative study of kala-azar vector control measures in Nepal. 2 Districts with 24 clusters. Alpha-cypermethrin was used in IRS, PermaNet for LLINs and lime for wall plastering.	LLIN effectively reduced the vector density and acted as insecticidal as well as repellent. Pyrethroid-based insecticides showed significant reduction in vector density. EVM appeared to reduce vector density but lacked long lasting results.	IRS, with proper supervision, was found to be the most effective measure to control vector density. LLINs were found to be a favourable alternative to IRS. EVM could not stand in for a long term control method, however it can be considered to be integrated with other interventions.
IRS	Diwakar et al., 2010	April-May 2008 (DDT) April-September 2009 (Deltamethrin) European Union/INCO-DEV KALANET	Analyse the sensitivity of <i>Phlebotomus argentipes</i> to 4%DDT and 0.05%deltamethrin on 60mins exposure time. 4 previously	DDT resistance was observed in one village which was on the border with Bihar, mortality-62%. Rest showed >90% mortality. Deltamethrin had 96-99%	DDT resistance was confirmed in villages on the border with Bihar. Susceptibility towards deltamethrin is high. IRS program requires proper management, training and

		project	reported endemic villages.	mortality in all four villages.	supervision in order to avoid resistance development.
IRS	Chowdhury et al., 2010	2008-2009 WHO/TDR	Analysis of the performance and effectiveness of lambda-cyhalothrin as a IRS. 2 Districts	Mean mortality of <i>P. argentipes</i> when exposed to deltamethrin was 97%. The IRS seemed to have a beneficial impact for 4 weeks. IRS program managers at district level were well aware of the technical guidelines however lacked in performance of spraying activities	Substandard spraying may contribute to development of insecticide resistance. Finer monitoring and timely identification and response of the shortcoming is required. Rapid test of sprayed surface for insecticide concentration at reasonable price can be useful in monitoring the performance.
LLIN	Picado et al., 2010	2003-2005 European Union (INCODEV/Project 015374)	Assessment of PermaNet LLIN in the reducing VL incidence using seroconversion. 3 Districts 5323 participants.	Risk of seroconversion: 3.1% (163/5323) Risk of VL after LLIN intervention was reduced by 10%	The results after the use of LLIN were not significant.
LLIN	Banjara et al., 2015	June - August 2013 WHO/TDR	Assessment of bednet impregnation with KOTAB 123 for	Untreated bednet: 89.3%; Regular bednet use: 67.7%; Sand fly	No significant change after insecticide impregnation which may be due to the

			vector control after 2 weeks and 4 weeks of impregnation . 300 households.	reduction: At 2 wks: 32.6%, At 4 wks: 12.5%	coverage done earlier as a part of vector control using IRS with pyrethroid.
Durable Wall Lining (EVM)	Huda et al., 2016	March 2014 - December 2014 WHO/TDR	Assessment of Durable Wall Lining (DWL) for vector control. 1 VDC DWL- Reduced Wall Surface Coverage (RWSC): 50 household DWL-Full Wall Surface Coverage (FWSC): 46 household	Both interventions had a significant decrease in sand fly density. Cost of RWSC was lower than FWSC.	DWL has the potential to be a long term vector control tool. Due to its cost-efficacy over FWSC, RWSC can be considered for the VL elimination program as it is also independent of house type, deployed IRS and baseline sand fly density.
IRS LLIN IWP	Banjara et al., 2019	June 2016 - August 2016 WHO/TDR	Assessment of vector control methods. IRS with deltamethrin 23%, KOTAB123 impregnated bednets and wall painting with Inesfly 5AIGRNG. 1 District (4	Twelve month sand fly mortality and effectiveness: IRS with deltamethrin - 23%, 1 month Bednet impregnated with KOTAB123 - 26%, 1 month Wall painting with Inesfly 5AIGRNG- 80%,	Wall painting with insecticidal paint can be considered as an alternative and sustainable strategy in the VL post elimination program.

			villages)	12 month	
EVM	Younis et al., 2020	2013 – 2017 WHO/TDR	Assessing the role of housing conditions and its environment in vector occurrence and transmission. 203 built environment (66 cases, 137 controls)	Adjusted odd ratio (AOR): Bamboo wall: 2.9; Walls made of leaves/branches: 3; Cracks in bedroom walls: 2.9; Sacks near sleeping area: 19.2; Kadam trees: 12.7; Open ground outdoor toilet: 9.3; Moisture in outdoor toilet shed: 18.09; Open land: 36.8; Moisture inside animal shed: 6.9; Surrounding animals/animal waste: 3.5	Elimination and educational programs should enforce awareness on housing improvement, risk factors of housing and environment contributing to VL transmission along with the protective measures against it.

VL case detection and surveillance

Regular reporting of the disease as well as analysis, review and feedback of information is needed to strengthen disease surveillance. Monitoring of the operational progress and the health impact is a vital part of disease elimination (Joshi et al., 2006). Various TDR funded studies have explored active case detection (ACD) and its different models with a similar conclusion that ACD is a cost effective approach appropriate for the elimination program (Joshi et al., 2006; Mondal et al., 2009; Hirve et al., 2010; Singh et al., 2011; Huda et al., 2012). Additionally, these studies also urged for the appropriate training, planning and strengthening of the referral services to overcome the challenges in the national VL elimination program. Consequently, ACD along with its standard operating procedures (SOP) was introduced in the 2014 national guidelines for VL. Strengthening ACD decreases the delay in diagnosis and treatment (Mondal et al., 2009; Hirve et al., 2010). Singh et al., 2011 in their TDR funded study conducted the assessment of different

strategies of ACD in order to understand the most cost-effective strategy and periodicity of ACD to be applied. In particular, the camp approach is recommended in high VL endemic areas, index approach in high to moderate VL areas and incentive approach in low endemic areas. Banjara et al., 2015 also emphasized the reinforcement of community health workers and team members involved. One of the early WHO/TDR funded studies conducted in rural Nepal has also highlighted the necessity of optimal use of the local health workers to encourage villagers to actively participate in the VL control program (Koirala et al., 1998). In the recent TDR study by Lim et al., 2019, it was found that delay in case reporting was 68 days in program districts and 83 in non-program (new foci) districts. Similarly, diagnostic delay for program and non-program districts was 38 and 36 days respectively. In order to facilitate a responsive intervention, awareness of VL is needed with prompt treatment along with timely and reliable information.

Presently, active case detection of VL through index case approach has been implemented in Nepal. Collaboration of public and private health care providers with adequate training can shorten the treatment delay. Providing training packages along with activities in health posts and pharmacies can help to make optimal use of the available human resources necessary to achieve and sustain VL elimination. In addition, it is necessary to forge partnership with the private sector (such as medical colleges, private practitioners and hospitals) for case detection and treatment through training and provision of services. In places where passive case detection (PCD) is weak, household screening with subsequent palpation of the spleen and rK39 testing by local health workers can be beneficial. Fever or skin lesion screening through integrated approaches followed by the distribution of ITNs can also be beneficial. Emerging challenges such as the geographical expansion of VL to new foci should be addressed early and the transmission dynamics in these foci should be analysed more extensively. Moreover, research on patients with subclinical infection is needed to understand the course of the disease. Identifying and reporting of relapses needs to be strengthened. The epidemiological shift of the disease also calls for the re-evaluation of the national guidelines and re-visitation of the previous endemic districts for investigation of current VL status. Additionally, research on the impact of climate change on VL disease and vector distribution is crucial to achieve as well as sustain the elimination. Active surveillance with contact tracing and mapping is necessary in the new focal areas. Evaluation of different VL elimination interventions can boost the prioritization and replication of those interventions in the government strategies. Furthermore, case based surveillance as well as vector surveillance should be established in the new foci. Population and vector surveillance within 500 m radius of every reported case in the new foci is worthwhile.

Table 4: Implementation research on VL surveillance

Surveillanc	Author	Year	Study Design	Result	Conclusion
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e Strategy	Year	Donor Engageme nt	Sample Size		
ACD: House Screening	Mondal et al., 2009	September 2006 - March 2007 WHO/TDR	Evaluate the health seeking behaviour for VL to provide baseline information for VL elimination program and explore potential for ACD. 1 District 37 villages, 2336 households	ACD: 37.5%; VL knowledge: 82%; Public sectors were preferred (45%) over private sectors (11%). 23% resorted to indigenous healers.	Monitoring operational progress and health impact is quintessential. ACD via house screening seems feasible however other models of ACD should be explored along with their operational cost. Training of unqualified health workers may help in early provisional VL diagnosis. Realistic policy response and monitoring of private pharmacies to prevent uncontrolled and inadequate drug use.
ACD: Index case-based; PCD	Hirve et al., 2010	January- May 2008 WHO/TDR	Assess the effectiveness and feasibility of ACD and PCD in VL elimination strategy. 57,713 population for screening	7 new VL cases. Total direct cost of ACD: USD1836. ACD is cost- effective when disease burden is high but passive surveillance is poor.	ACD can be a cost- effective approach supporting PCD. It decreases delay in diagnosis and treatment. Further research is needed to determine the predictability of such strategies and alternative cost- effective approaches. Combination

					approaches that are cost-effective, sustainable and adaptable to the situation are beneficial for the elimination program.
ACD: - Camp -Blanket approach -Index case approach -Incentive approach	Singh et al., 2011	May-December 2009 WHO/TDR	Assess the feasibility, cost and effectiveness of 4 different ACD strategies. 2 rounds 6 months apart. 1 district with 5 per 10,000 VL incidence. Overall, no of camps: 12	Round 1 Camp: New VL cases- 5, Sensitivity- 100%; Blanket: New VL case- 5; Index: New VL cases- 0, Sensitivity- 0%; Incentive: New VL cases- 4, Sensitivity- 100%; Cost per camp (USD): 195; Round 2 Camp: New VL cases- 3, Sensitivity- 100%; Blanket: New VL case- 3, Index: New VL cases- 0, Sensitivity- 0%.	Adapting camp approach in high VL endemic areas, Index approach in high to moderate VL endemic areas and incentive approach in low VL endemic areas is recommended. It is cost-effective to have trained health workers able to perform both spleen examination and RDT in the team.
ACD: -Camp -Index case-based	Huda et al., 2012	July 2010 - April 2011 WHO/TDR	Assess the feasibility and performance of ACD strategies in national program.	Camp strategy submitted 3 new VL cases. One camp lacked adequate supply of rK39	ACD can be adapted into the national program, however its challenges have to be overcome via appropriate training, planning

			2 Camps and 45 Index case searches at 37 VDCs in endemic areas.	for testing. No new case from Index case search strategy. Cost of detecting the new VL was USD 199.	and strengthening of the referral service.
ACD -Combined Camp	Banjara et al., 2015	June - August 2013 WHO/TDR	Assess the feasibility and result of ACD via combined camp strategies. 1 District (annual VL incidence 0.7 per 10,000 population) 85 febrile participants.	New VL case: 1; Cost per combined camp: USD 125.15; rK39, drugs and other supplies for VL treatment were available in district health facilities. Health workers at primary health care have received training regarding VL.	Combined fever camps seem to be feasible however the cost for the health services needs further thoughts. Cost-efficacy can be achieved when combined camps are part of routine operations with team members knowing their roles and responsibilities along with community health worker involvement.
Passive Surveillance	Boettcher et al., 2015	July - September 2012 WHO/TDR	Assess the passive surveillance and analyse the duration required for reporting of VL cases from district to central health authorities. 12 Districts of Terai region. 13 hospitals.	Seeking Health care- 30 days; Receiving VL diagnosis- 25 days; Receiving treatment- 3 days; No of consultation: 1.4 Reporting of VL case- 77 days	Implementation of the electronic VL reporting system and close link to HMIS at central level can be beneficial.

			46 VL patients		
Passive Surveillance	Lim et al., 2019	February-May 2016 WHO/TDR	Assess the surveillance and reporting system requiring strengthening 40 VL patients	Delay reporting: Program district- 68.5 days, Non-Program district- 83 days; Diagnostic Delay: Program district- 38.5 days, Non-Program district- 36 days; Reporting Delay: Program district- 45 days, Non-Program district- 36 days.	Awareness of VL along with ensuring prompt treatment, timely and reliable information is needed to facilitate a responsive system of interventions.
ACD (Incentive approach)	Omer et al., 2020	June - August 2018	Analyze the existential and potential role of FCHV in VL elimination as well as community awareness and protective measures against VL. 22 VL endemic villages of 3 districts.	Support from family and incentives were enabling factors to accomplish their duties. FCHV in terai region were more aware of VL than those of hilly region. Communication gaps between FCHV and health officials were present. Financial and	FCHVs play an important role in the VL elimination program as they are living in the community and their participation can make the program more sustainable and efficient. Formal training, family support and incentives can help FCHVs to be more efficient. There is still a need for

			203 households	deficient infrastructure influenced the treatment seeking. Knowledge of VL was better in households with a history of kala-azar than those without.	awareness of VL disease and its transmission-prevention and treatment, especially in hilly regions which should be promoted through appropriate media, FCHVs and health workers in the community.
Passive Surveillance	Cloots et al., 2020	October-December 2016 The Directorate-General for Development Cooperation of Belgium	Assessment of L. donovani transmission since the launch of VL elimination initiative by repeat survey in population below 2 years and older with baseline serological data from 2006.	Sero-prevalence was lower in 2016 as compared to 2006 in all repeated clusters among all age groups. Adjusted risk ratio of 2016 in comparison to 2006 for seropositive: 0.44	Current surveillance is based on monitoring of disease incidence; nevertheless monitoring of infection would permit more accurate surveillance of transmission allowing timely control measures to prevent resurgence.

Visceral Leishmaniasis Recording and Reporting System

Before 2015, the number of treated VL cases were reported directly through the EWARS sentinel sites to EDCD. Along with this, the VL data were also recorded in DHO/DPHO which were then further reported to the RHD and EDCD through HMIS on a monthly basis.

Visceral Leishmaniasis surveillance system

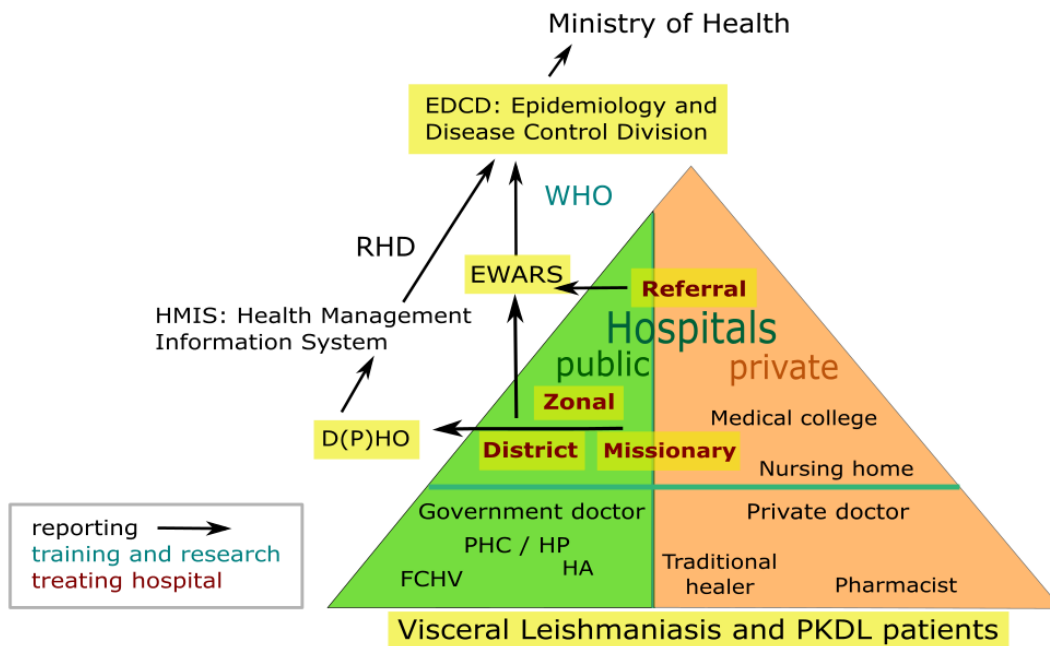


Figure 1: Structure of the surveillance system in Nepal before 2015 (EWARS= Early Warning and Reporting System; PHC= Primary Health Care; HP= Health Post; HA= Health Assistant; FCHV= Female Community Health Volunteer; D(P)HO= District (Public) Health Office; RHD= Regional Health Directorate)

Currently after the country's restructuring in 2015 which involved the health system, the community level health facilities are under the rural or urban municipalities. The data is obtained by DHO from rural and urban municipalities. Similarly, rural and urban municipalities report to the provincial health directorate as well as to EDICD and VBDRTC. They also report the monthly aggregated data to the iHMIS section of DoHS through the DHIS2 electronic reporting system. Likewise, EWARS sentinel site hospitals also report directly to EDICD immediately or on a weekly basis.

Private hospitals can diagnose the VL cases but in case of treatment they are referred to the government hospitals. Therefore they are not included in the surveillance system.

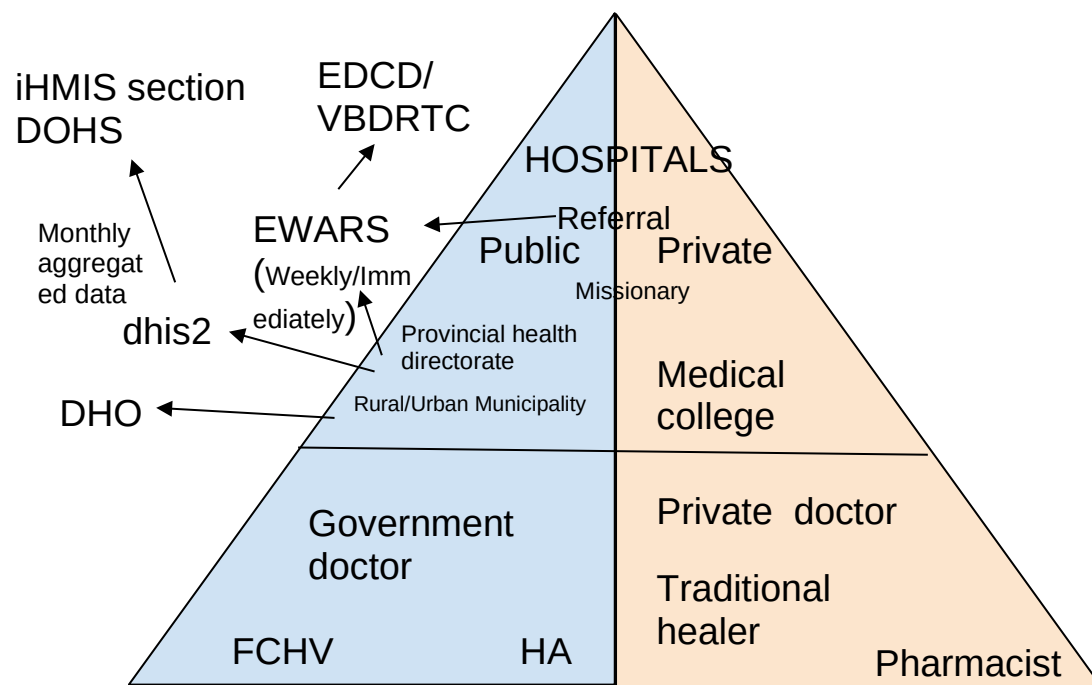


Figure 2: Structure of surveillance system in Nepal since 2015 (EWARS= Early Warning and Reporting System; PHC= Primary Health Care; HP= Health Post; HA= Health Assistant; FCHV= Female Community Health Volunteer; DHO= District Health Office; WHO= World Health Organization; HMIS= Health Management Information System)

Capacity Building

In 2012, PHIDReC in co-ordination with EDCD organized an in-country training workshop on VL for medical officers, public health administrators and vector control officers involved in the VL elimination program. This training workshop was financially supported by WHO/TDR. The objective of the training was to build capacity for monitoring and evaluating vector control specifically through IRS with adequate mechanisms along with ACD complementary to passive surveillance in highly endemic areas.

TDR has also supported capacity building by providing Research Training Grants (RTG) in epidemiology, medical microbiology, economics and laboratory sciences. VL is one of the diseases covered by the RTG recipients. The research results conducted by RTG recipients have been of great significance for researchers and policymakers. Particularly, VL research with special reference to the cross border problem made notable contributions to the understanding of the sero-epidemiology of the disease. Besides this, TDR also provided Research Capacity Strengthening (RCS) grants which helped former RTG recipients to continue their research efforts. It has also been successful in bringing local and international collaborators in touch with Nepalese researchers in order to build local capacities in research and training in tropical diseases. The WHO country office financially supported and trained all VL treating physicians in the use of Miltefosine in 2009 and in the use of Liposomal Amphotercin B in 2019. KALACORE has also supported capacity building through the training of FCHVs on VL elimination. Apart from this, FAIRMED, a Swiss NGO working in Nepal since 2015 has been focusing on the integration of NTDs and maternal and new born health at primary health care level, which also partly included work on VL.

Major policy changes for VL with timeline

WHO/TDR has contributed to eliminate VL through providing technical and financial support to conduct implementation research (Annex 2; Annex 3; Annex 4; Annex 5; Annex 6).

One of the early research projects supported by WHO/TDR described people's knowledge, attitude and practice regarding VL in rural Nepal. The data obtained from this study helped in planning and evaluating VL related control activities.

Direct agglutination test was introduced into the national control program in 1995. Later on, based on the findings from the TDR supported research on the rK39 test (from 1990 to 2008), rK39 was introduced as a confirmatory test in the national VL elimination program in 2005.

SSG was the drug of choice (as monotherapy) introduced into the national VL control program in 1994. Amphotericin B was in the national control program since 1994 as a second line drug. Later in 2019, it was recommended as a fourth line treatment option in the national VL elimination guidelines. In 2008, miltefosine, an oral monotherapy, was introduced into the national VL elimination program as the first line regimen after the phase III trial in India, and later on, the phase IV trial of miltefosine conducted with the support of TDR in Nepal in 2009. Since 2014, miltefosine is used as a second line regimen in combination with paramomycin and L-AmB. In 2019, oral monotherapy with miltefosine was listed as fourth line regimen. Through the series of positive outcomes from the research projects conducted in India, L-AmB was introduced into Nepal's VL treatment protocol in 2014 and has since 2015 been a first line therapy in the national VL elimination program in the country. Combined therapy was introduced into Nepal's national treatment protocol in 2014 based on the favourable results obtained from the series of TDR supported research projects since 1995 in India. Combined therapy consisted of a combination of L-AmB and miltefosine or L-AmB and paramomycin or miltefosine and paramomycin. In 2019, paramomycin, as a monotherapy, was introduced as a fourth line regimen into Nepal's national VL elimination program on the basis of research conducted in India since 1995.

The Ministry of Health in Nepal started IRS for VL control with lambda-cyhalothrin insecticide in 1992. IRS was applied in villages that had reported VL cases in the previous year as per the national IRS policy. DDT was last used in IRS in 1993 after which it was abandoned. As the TDR study conducted by Joshi et al., 2003 between 1991 and 2001 revealed development of resistance to DDT, rotation of synthetic pyrethroids was put in place after 2002. In 2003, alpha-cypermethrin was used as an insecticide for IRS and lambda-cyhalothrin was reintroduced in 2007 and used until 2011. As a part of rotation, alpha-cypermethrin was used in the year 2012 and 2013 followed by Deltamethrin in 2014 to 2016. Lambda-cyhalothrin has been in use from 2017 to 2020. The TDR funded studies done by Joshi et al., 2008 and Joshi et al., 2009 showed the importance of IVM in VL elimination, which eventually led to its inclusion in the national elimination program in 2010. Data collection forms developed by researchers have been adapted by the national VL elimination programme for vector control activities (Annex 9, 10, 11).

In 2014, active case detection (ACD) was incorporated into the national guidelines for VL elimination. Standard operating procedures for different methods of ACD were developed through TDR supported research and were also adopted in 2014 and 2019 into the national guidelines of the VL elimination program. The SOPs for ACD include SOPs for index case based approach, camp approach and incentive based approach (Annex 8). The forms for active case detection activities were developed by the researchers and have been adapted by the national

VL elimination programme for active case detection through index case based approach (Annex 12), camp based approach (Annex 13) and case referral (Annex 14).

Every year, TDR supported meetings of researchers and program managers of Bangladesh, India and Nepal were held to discuss research findings and how to translate research into national guidelines and regional strategies for the VL elimination program. These annual meetings of program managers and researchers were organised in the participating countries, in Geneva or in Freiburg. In these annual meetings, new findings were disseminated and the objectives for the next research phase identified (Annex 4; Annex 6). Subsequently, researchers were invited to develop and update the national guidelines on VL elimination and to also participate in RTAG meetings.

Regional Technical Advisory group (RTAG) on visceral leishmaniasis

In order to assist the elimination of VL in the South East Asian Region, SEARO established a Regional Technical Advisory Group (RTAG) on VL in 2003 to advise WHO and member countries on ways and means to accelerate VL elimination activities in the region. The objectives of the RTAG on VL were as follows:

1. To advise the Regional Director, WHO SEARO on policies, strategies and activities that is crucial for accelerating elimination of VL.
2. To advise on directions, to identify weaknesses and to provide recommendations on VL elimination strategies.
3. To identify the strength and weakness of the elimination strategy and to make recommendations
4. To advise on the use of appropriate and new technology for effective elimination of VL.
5. To advise the Regional Director and member countries on various aspects of research on VL including operational research.

Since the signing of the Memorandum of Understanding (MoU) between VL endemic countries in 2005, many RTAG meetings have been conducted. RTAG VL consists of 13 independent experts selected on an individual basis for their expertise in VL and related fields. The RTAG members are appointed by the Regional Director. The group comprises of experts in the fields of epidemiology, entomology, communications and social mobilizations and includes delegates from major endemic countries. The RTAG meeting held on 5-8 October 2020 was virtual due to COVID 19 pandemic. The recommendations given were in the following areas:

- Review the validation process, its requirements and preconditions to be met for declaration that a country has reached its target of VL elimination as a public health problem (<1 case per 10000 population with zero death)

- Support and facilitate a time to time evaluation of the elimination program
- Sustenance of drug donation in the post elimination phase
- Plan for the renewal of the MoU for the elimination goal among member states in the region
- Country guidance for the VL program in line with the new WHO NTDs roadmap 2021-2030
- Guidance on rolling out of the new VL-HIV treatment guidelines

Member countries of the SEA region were cautioned to ensure continued implementation of VL elimination program activities while taking necessary precautions during the COVID 19 pandemic. Continued village focused intensified case detection and vector control activities have been emphasized. Member countries were also advised to prepare the validation process for the declaration of the elimination of VL as a public health concern.

The most recent RTAG meeting held in April 2022 noted that despite the remarkable progress, “current tools and case finding strategies are not optimal to move towards elimination of transmission”. It urged WHO to:

- finalize the WHO dossier template for validation of elimination of VL as a public health problem and orient and support national programmes in the requirements and preconditions to be met for validation process.
- launch the new regional strategy for VL elimination in South-East Asia whose core principle will be “strong government ownership and effective integration of surveillance, clinical management and vector control interventions against VL into other public health programmes and routine work of PHC workers and front liners as a key for sustainability in the post-validation phase”. The RTAG stressed that “continued actions are required to maintain the targets after validation of elimination as a public health problem is achieved”
- advocate and promote innovation and research to support national programmes in accelerating VL elimination
- convene a high-level advocacy meeting to re-visit the extension/renewal of Memorandum of Understanding for continuing political commitment, Regional cooperation to eliminate Kala-azar from the South-East Asia.

Table 5: Major strategic changes in the VL control/elimination program in Nepal

Particulars	Introduced in National Elimination Program
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Diagnostic Tool	
Direct Agglutination Test	1994
rK39	2005
Treatment	
Liposomal Amphotericin B (Monotherapy)	2014 introduced into the national treatment protocol. 2015 as first line therapy
Miltefosine (Oral Monotherapy)	2008 as first line regimen 2019 as fourth line regimen
Amphotericin B deoxycholate (Monotherapy)	2019 as third line regimen
Paromomycin (Monotherapy)	2019 as fourth line regimen
L-AmB 5mg/kg (single) + Miltefosine 50mg BD (7 days) OR L-AmB 5mg/kg (single) + Paromomycin 11mg/kg (10days), OR Miltefosine + Paromomycin (10 days) (Combination therapy)	2014 introduced into the national treatment protocol as second line treatment
Sodium Stibogluconate (Monotherapy)	1994 as first line regimen
Vector Control	
IRS with Lambda Cyhalothrin (ICON), DDT, Malathion	1992 till 2002
IRS with Alpha Cypermethrin	2003
IRS with Lambda Cyhalothrin (ICON)	Reintroduced in 2007
IRS with Alpha-cypermethrin	2012
IRS with Deltamethrin	2014
IRS with Lamda Cyhalothrin	2017 till 2020
LLINs distribution	2009

IVM	2010
<i>Surveillance</i>	
Active Case Detection	2014
SOP for ACD	2014

Success of the elimination program: Decreasing VL trends in Nepal 2002-2020

In 2003, Nepal witnessed its highest case load of VL. In the same year, the rotation of synthetic pyrethroids was introduced. Since then, the overall burden of VL cases has decreased significantly. The numbers of cases and death rates have dropped drastically since the VL elimination initiative started in 2005. In 2008, miltefosine, an oral drug, was introduced as a drug of choice (and as monotherapy) for VL in the elimination program. Thereafter, the number of cases decreased in comparison to previous years. This could be due to the oral route of administration influencing patient compliance to treatment. Distribution of LLINs, in addition to IRS was also introduced in 2009, which also helped decrease the VL burden in the country. ACD was introduced in the VL elimination program in 2014. However, it has not been effectively implemented. In recent years, the number of deaths has increased probably due to transmission of VL in the new foci. Overall however, the number of VL cases has decreased by 90% in 2020 as compared to 2002, which could be due to the synergistic impact of all interventions of the VL elimination program.

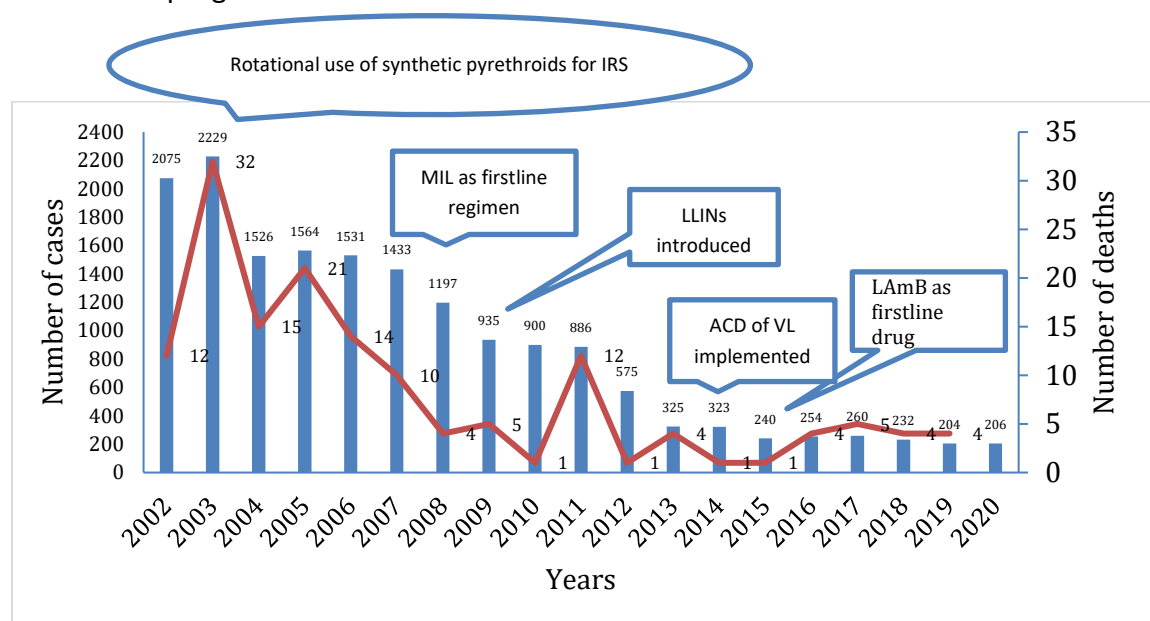


Figure 3: Trend of VL cases and deaths, 2002-2020

Priority research areas for VL for the next ten years (consolidation and maintenance phase)

The five pillars of the VL elimination strategy are: early diagnosis and complete treatment; integrated vector management and vector surveillance; effective passive and active case detection for disease surveillance; building partnerships and social mobilization; continuous clinical and operational research.

The following are the priority areas for implementation research identified in the consultative meetings with stakeholders, including national programme managers held in 2021:

Early diagnosis and complete treatment

Short term:

1. Study on VL relapses in newly treated cases as well as identification of parasite resistance towards anti VL drugs. Relapse and treatment failures should also be retrospectively analysed based on the pattern of the treatment.
2. Due to the changing presentation of VL, rK39 should be validated in areas of new foci.
3. Analysis of data on HIV-VL co-infection.

Medium term:

4. Longitudinal observational study of the prevalence of Hemophagocytic Lymphohistiocytosis (HLH) in paediatric VL cases is suggested. Clinicians treating VL cases have reported changes in VL presentation with the majority of the VL cases currently being in the paediatric age group.

Long term:

5. Development and validation of non-invasive antigen-based diagnostic tools.

Integrated vector management and vector surveillance

Short term:

1. Vector identification, monitoring insecticide resistance and vector bionomics in different ecological areas.

Medium term:

2. Vector surveillance and determination of the infection rate in sand flies in new foci and in previously endemic areas in the perspective of changing ecology and climate patterns.

Disease surveillance

Short term:

1. Determination of the role of migrant populations in VL transmission through screening at border posts.

Medium term:

2. Investigation and longitudinal follow up of the clinical course of VL progression from asymptomatic to symptomatic, the role of domestic animals in its transmission together with risk assessment in previously non-endemic areas in the maintenance phase of elimination.
3. Research on the influence of climate change on VL disease and vector distribution to determine the dynamics of both the disease and the vector.
4. Establishment of the diagnostic markers at population level to verify VL elimination.

Long term:

5. Integration of the surveys combining the leishmanin skin test or DAT and rK39 rapid immunochromatographic test to monitor VL transmission in low incidence areas.

Capacity building and social mobilization

Short term:

1. Evaluation of the effectiveness of VL awareness activities in new foci.
2. Socio behavioral research on the occurrence of VL in new foci.
3. Detection rate of VL in new foci after training the local health workers.

Plan for transitioning towards sustainable internal resource leveraging for continued implementation research in support of zero VL

In previous years, VL research was primarily supported by partners among which WHO/TDR and the European Union were the major financial contributors to VL implementation research in Nepal. From 2021, the government of Nepal allocated around 100 million Nepalese rupee (equivalent to about 800,000 USD) annually through the Nepal Health Research Council (NHRC) to finance different research activities in the country. EDCD has also allocated funds from the program budget for VL drug resistance monitoring and research on cutaneous leishmaniasis for the year 2021-2022. Since VL elimination is a national strategic goal, NHRC should allocate specific funds for VL research on priority areas to support the VL elimination program. Furthermore, EDCD can mobilize the program budget to conduct implementation research to support program activities. Although the government has started to allocate domestic funds for

research on VL, the amount provided is insufficient for the volume of implementation research the maintenance phase of the VL elimination would likely require. Therefore, continued partner support is essential to fill the funding gaps in the priority implementation research areas on VL.

The budget has been divided into four key areas of need: diagnosis and treatment, vector management and vector surveillance, disease surveillance and capacity building and social mobilization. The proposed budget for implementation research for the period 2022 - 2025 is 3.7 million USD of which the MoH and EDCC can cover 1.8 million USD leaving a funding gap of 1.9 million USD. Similarly, for the subsequent five year period (2026 – 2030), total funds required for VL implementation research is around 4 million USD. The MoH and EDCC plan to cover 1.9 million USD and the funding gap will be 2.1 million USD.

Conclusion

For the development of this report, key VL documents on the national policy and elimination strategy, published and unpublished implementation research reports and scientific publications were reviewed. consultative meetings and workshops were organized with policy makers, researchers, clinicians treating VL, entomologists, programme staff and development partners working on VL elimination to document the impact of implementation research on the elimination strategy and to propose key areas for the next phase of research activities related to the consolidation and maintenance phase. The priority areas for further research were identified in consultation with the national programme, researchers and other stakeholders and a guideline/proposal on how this could be funded has been developed. The document will assist Nepal in leveraging resources and would be a useful input for funders to formulate their exit strategy without creating gaps that would risk a reversal of the gains made so far. The review document presented here has identified priority areas for implementation/operational research in support of programmatic activities to consolidate and sustain VL elimination. Further, it is intended to indirectly support member countries in the WHO South East Asia Region in preparing their dossiers for WHO validation of VL elimination with a specific timeline and advocacy plan.

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Annexes

Annex 1: List of participants

Workshop on an assessment of the impact of mplementation research on VL elimination efforts in Nepal: National perspective (23-27 September, 2021)

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Annex 2: Agencies and institutions conducting VL research since 2000

Agencies supporting research funding

- TDR
- WHO
- DNDI
- DFID
- ASCEND
- KALACORE
- FairMed (Swiss organization), Nepal
- European Union
- Institute of Tropical Medicine, Antwerp, Belgium

In country

- Institute of Medicine, Tribhuvan University, Kathmandu
- BP Koirala Institute of Health Sciences, Dharan
- Epidemiology and Disease Control Division, Kathmandu
- Nepal Health Research Council, Kathmandu
- Vector Borne Disease Research and Training Center, Hetauda
- Public Health and Infectious Disease Research Center, Kathmandu

Annex 3: VL publications from studies in Nepal

VL Policy brief paper

1. UNICEF and World Health Organization, 2010. *Research to support the elimination of visceral leishmaniasis: annual report 2009* (No. TDR/BL10. 10). World Health Organization.
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Annex 4: Number of VL publications by year and category

Year	Topic	TDR supported/funded	Other than TDR supported	Total
1990-2000	VL treatment	2	1	3
	Diagnosis			
	Vector Control			
	Surveillance	1		1
2001-2010	VL treatment	1	3	4
	Diagnosis	2	4	6
	Vector Control	3	5	8
	Surveillance	2		2
2011-2020	VL treatment	1	5	6
	Diagnosis	1	4	5
	Vector Control	11	2	13
	Surveillance	18		18

Annex 5: WHO/TDR supported VL implementation research conducted by the Institute of Medicine, Tribhuvan University

Year: August 2006 - April 2007
Title: To develop improved implementation strategies for early case detection and treatment of all VL patients.
Objective: To develop improved implementation strategies for early case detection and treatment of all VL patients.
Study design, Sample size: Systematic random sampling. 36 Kala-azar endemic VDC and 1 municipality of Mahottari district. 2336 households. 17239 participants. 82 formal and informal healthcare providers.
Finding: 6 new VL cases. Public consultant: 60%, Private consultation: 20%. Delay between appearance of signs and diagnosis: 88.8%. Delay for diagnosis and treatment: 22.2%. rK39 was the main source for diagnosis. SAG and Amphotericin B was the choice of treatment. Both clinical and laboratory results were used for the diagnosis of KA. 57% of VL patients were labourers.
Conclusion: Knowledge on KA and its modes of transmission, prevention and control is limited. Even though the government had subsidized the cost of VL treatment and diagnosis, patients still had to pay service-obtaining costs. This plays as an economic burden to them as the majority of the patients are labourers and the rest depend on agriculture. Finding from research suggests strengthening of peripheral health facilities as well as extensive study on active and passive case detection and economic impact of KA

Year: September 2006 - April 2007
Title: Efficacy and cost of Indoor Residual Spraying (IRS) Insecticide Treated Nets (ITNs) and eco-environmental control measures for VL vectors in Nepal (Phase I)
Objective: To evaluate the effectiveness of different interventions for VL vector management (IRS, LLINs and ecological intervention EVM) in a comparative way in order to inform policy about different VL vector control options.
Study design, Sample size: Cluster randomized trial design. 4 VDCs from Sarlahi districts. Household covered for EVM: 188, IRS: 210, LLINs:244. Total population: 5505
Finding: Baseline and Post intervention density of sand fly by CDC light traps in: Control- 18.13 & 33.90, EVM- 20.60 & 25.80, IRS- 18.66 & 25.20, LLINs- 17.10 & 29.07; LLINs (mortality within 60 mins): 1 and 6 weeks- 100%, 4 months- 70%; IRS (mortality within 60 mins): 1 and 6 weeks- 100%, 4 months at insecticide sprayed mud plastered surface- 60-70%; 95% thatched roof houses, 17% no doors houses, 39.9% one door houses, 88% no window houses, 68% no housing compound, 60.8% houses less than 10 meters from animal shed, 98.4% plastered one or two times a year with mud and cowdung (92%), cowdung and lime (8%). Average sand fly growth rate reduction after intervention:

EVM- 61.71%, IRS: 61.78%, LLIN: 16.97%. Total cost (NRS) of: EVM- 84130, IRS- 72689, LLIN- 214608.

Conclusion: Consequential difference observed between IRS and EVM with control group. No significant mean difference between LLINs and control. LLIN and IRS had 100% mortality of sandflies till 6 weeks after intervention but reduced to 50-60% after 4 months of intervention. The interventions were accepted by the community people. At initial phase, IRS is the most cost-effective intervention however the cost effectiveness of the intervention changes with different phases.

Year: July 2008

Title: Validation of conventional and newly developed indicators and procedures for monitoring vector control in VL elimination program (Phase II)

Objective: To assess and develop the indicators to monitor and evaluate the progress and impact of IRS and LLINs in vector control program towards VL elimination

Study design, Sample size: Study conducted in Sarlahi district. LLINs distributed in 6 clusters and IRS in 4 VDCs from intervention cluster. Data collected via interviewing related personnel. Vector control guidelines, published/unpublished government documents and other published articles and documents were reviewed.

Finding: The vector control guidelines have sufficient number of guidelines. Spraying is carried out in two cycles, first in April/May and second in August/September. Insecticide is selected based on the cost and effectiveness in comparison to past spraying and are procured by the government. Spraymen only use mask, gloves and cap while spraying and are not provided with body covering dress, shoes and spectacles. District lacked in spray pump amount. Among the forty households provided with LLINs, 77.5% washed their bednets. Mortality in washed LLINs: 49.6%, non-washed LLINs: 62.7%. Baseline mean sand fly densities in control: 67.58, IRS intervention: 42.83%. Post IRS intervention after 4 weeks: 15.61. Toolkit of indicator for monitoring VL control program includes Input and Process. Input consists of guideline and action; availability of insecticide and its storage, distribution, availability, protective measures and allocation of correct target concentration; quality of chemical certified; and training capacity building. Process consists of observed skills of sprayers/dippers, observed supervision of spraying/dipping, routine susceptibility testing WHO test paper, observed insecticide management, number of HHs sprayed per pump per day and grams of insecticide per HH (Details on the toolkit indicator is mentioned in the annex).

Conclusion: Guidelines have covered most of the activities however, its implementation in selection of spray men and safety measures while spraying, training, community participation and releasing budget in time is substandard. LLINs coverage in the community is low but its use and acceptability is very high. Coverage of IRS is relatively higher and well accepted too yet not all risk areas are fully covered. Toolkit of indicators has been developed for the VL vector control program after analysing the other indicators

Year: July 2008
Title: Implementation research for an improved strategy of diagnosis, treatment and follow-up of kala-azar patients (Phase II)
Objective: This is a second phase follow up study devised to develop improved strategy of diagnosis, treatment and follow-up of kala-azar patients.
Study design, Sample size: 3 kala-azar endemic districts were selected for ACD and PCD. 15247 participants from 3049 HH selected based on index case approach reported from PHC, zonal and tertiary hospitals. Cases reported with fever >15 days with clinical signs were screened with rK39 dipstick test. For PKDL cases, rK39 test was done.
Finding: Prevalence of KA: 3.5 per 10,000. KA cases in last one year among screened population: 25 (0.2%). Fever > 2 weeks: 47 (0.3%). KA positive by rK39 test among total fever cases: 25 (53.2%). ACD based on index case: 5. 25 KA positive cases eligible for miltefosine: 6 (24%), Amphotericin B: 13 (52%), SAG: 6 (24%). Seeking health care after start of fever: 50.84 days; Receiving VL diagnosis: 7.36 days. Mean number of days for seeking health care after the start of fever, start of diagnosis and start of treatment were lowered in ACD in comparison to PCD.
Conclusion: 5 new cases were detected via index case approach. In field setting, 25 positive rK39 test were found. Among those positive cases, 6 were eligible for miltefosine, 13 for amphotericin B and 6 for SAG. Health seeking behaviour were relatively better in ACD than PCD.

Annex 6: PHIDReC VL research supported by WHO/TDR

Year: March 2010
Title: Towards more cost effective VL case detection and case management in endemic district (Phase III).
Objective: To analyze the feasibility, cost, results, organizational aspects and frequency of alternative approach of ACD - camp approach, blanket approach, focal approach and incentive based approach in different field settings.
Study design, Sample size: Study conducted in Sarlahi. Two VDCs with 40,799 population selected for camp + blanket approach, four VDCs 41,303 population for incentive based + blanket approach carried out by FCHVs. Two rounds of health camps (second round after six months of first round. Incentive based and drug sellers for four months followed by blanket approach.
Finding: 8 VL cases detected in both round by camp approach. 4 VL cases detected by incentive approach and referred by the FCHV. Zero cases detected in house to house screening, four months after incentive approach. 24 cases detected from through index based approach.
Conclusion: Camp based approach is suitable only for a particular point of time to cover VL cases. It cannot cover the cases developed in continuum trend. As the cases were found to be developed within long duration, the time point for the induction of index base approach is not definite. Incentive based approach appeared to be more feasible, applicable as continuous phenomenon and effective method to detect all of the cases developed during the course of time.

Year: March 2010
Title: Usefulness, feasibility and cost of vector control monitoring in Kala-azar endemic districts (Phase III).
Objective: To assess the usefulness, feasibility and cost of the district monitoring systems at different levels using the set of indicators established in Phase II as well as assessing the KAP and management of IRS operation by spray team.
Study design, Sample size: 3 kala-azar endemic districts Sarlahi, Mahottari and Dhanusha were selected. 4 VDCs from each district were selected randomly. In depth interviews with the vector control manager were taken regarding the selection of spray, insecticide preference, timing of the spray, transportation, storage, equipment and handling of insecticides as well as availability of guidelines, disposal practices and training in relation to the control measures. This was conducted through observation and vector density monitoring and bio-assay.
Finding: Lambda-cyhalothrin (Ticon) insecticide is used for spraying. Interval between two spray cycles: 3 weeks in Sarlahi and Dhanusha, 3-13 weeks in Mahottari. Average houses covered by spraymen: 7 in Dhanusha, 5 in Sarlahi and 6 in Mahottari. Average quantity of insecticide used in grams per person: 14g in Sarlahi, 10g in Dhanusha. Training of spraymen before spraying in all 3 districts: 100%. Duration of training: 15-30

days. Protective gear used while handling insecticides: Mask: 83.3%, Gloves: 16.7%, Coat apron: 16.7%, Boots: 100% and Goggles: 100%. 100% of people received advice from spraymen to stay outside the house during spray. 100% availability of enough spray pumps and spare parts for pumps in all districts. Storage adequacy: Sarlahi 100%, Dhanusha 50%. All 3 districts had 100% availability of record forms, timely reporting, completeness of records and accuracy of the form. Total mean count of *P. argentipes* in control arm: 4.05 for baseline, 17.13 after 2 weeks, 17.81 after 5 months in total. Total mean count in intervention arm: 3.75 for baseline, 2.50 after 2 weeks, 6.38 after 5 months. Total mean corrected mortality rate post IRS after 2 weeks: 100% in both mud and wood; after 4 weeks: 78.1% in wood and 62.6% in mud; after 5 months: 18.3 in wood and 6.7 in mud. 56% of people use LLIN year round, 57.9% did not wash LLINs, 40.4% washed twice or thrice using soap and soda. Total cost (USD) of Monitoring: 1,706; Routine susceptibility: 1433; Bio essay test: 2,034.

Conclusion: IRS coverage is relatively higher and well accepted. However, it still lacks in fully covering risk areas. Vector densities were found to be similar after 2 and 4 weeks after spray but increased in 5 months of spray. Mean corrected mortality rate in wood and mud had no significant difference in 2 weeks but in 4 weeks and 5 weeks, there was a significant difference between wood and mud surface. In all districts, information on observation for spraying activities were up to the mark. Pumps were well filled by the spraymen with no leakage however well fitted pressure gauze of pump was substantially low in Sarlahi and Dhanusha districts. Regarding safety measures, all sprayers used masks but other safety items were only used by few.

Year: February 2011

Title: Evaluation of the Feasibility and Usefulness of a Monitoring and Evaluation (M&E) Toolkit for Visceral Leishmaniasis Vector Control in National Programmes (Phase IV)

Objective: To contribute an effective IRS programme in the context of VL elimination initiative through the evaluation of a newly developed monitoring and evaluation toolkit which guides programme managers to respond quickly to different programmatic shortfalls.

Study design, Sample size: 5 Kala-azar endemic district i.e. Mahottari, Dhanusha, Sarlahi, Rautahat and Bara were selected. Standardized training was held for program managers regarding the use of M&E toolkit. In order to collect information on input, process, output and outcome indicators, self-administered questionnaires to program managers, focus group discussion, observation of spraying, interview of the community people on acceptance of spraying were performed in the selected districts. Vector density was monitored at baseline, two weeks, four weeks and four months after spraying. Bio-assay was performed after two weeks, four weeks and four months post spraying.

Finding: All districts had guidelines, action plan, required amount of insecticide, IEC materials and regular supervision in place but lacked in required number of functional pumps, spare parts, protective measures for sprayers. There was conventional

supervision in place in all districts but the information collected during supervision weren't systematic neither were they analysed. Community satisfaction was present. Vector density reduced to 65% in two weeks, 43% in four weeks and 28% in four months after spraying in comparison to the baseline.

Conclusion: For the spraying activities to be effective, there is need for an improvement on the supervision of the activities to assure quality spraying. In addition to this, systematic as well as complete recording and reporting of the information is essential.

Year: February 2011

Title: Implementation Research for Enhanced VL Case Detection and Improved Case Management by the National Kala-azar Program in Bangladesh, India and Nepal (Phase IV)

Objective: To enhance the VL case detection and improved case management by the national KAAP through implementation research in relation to the newly established case detection/ case management strategy.

Study design, Sample size: 3 VL endemic districts – Sarlahi, Dhanusha and Mahottari were selected. Health workers were interviewed regarding the prospect and constraint of camp and index case approaches of ACD as well as the treatment of VL using miltefosine. 22 patients were interviewed regarding their satisfaction to the services they received during the treatment. Three hospitals and five Primary Health Care (PHC) centers were observed for the availability of the diagnostic kit and drugs for VL as well as other facilities for the treatment. 309 people were screened for VL via camp approach in two VDCs while 7091 people were screened based on the index case approach.

Finding: Out of 309 people screened, three were found rK39 positive and referred to the Sarlahi District Hospital. Treatment by amphotericin B was four times higher than treatment by miltefosine. Out of five PHC, only one had facilities for the VL case management. All the interviewed patients were satisfied with the treatment they were receiving from the public hospital.

Conclusion: Camp approach can be used in high endemic areas. More training of peripheral level health care providers along with the co-ordination to use miltefosine for VL treatment at home is required.

Year: September 2013

Title: Feasibility of a combined camp approach for active case detection of VL/PKDL including other fever diseases and vector management.

Objective: To determine the feasibility of combined research camps for active case detection of VL and bed net impregnation for the control of VL.

Study design, Sample size: Cross-sectional evaluation study was conducted. VL endemic district Saptari was selected. 4 villages of Saptari with 18 VL cases were chosen. ACD was conducted through "chronic fever" camp approach together with vector control by distributing bed net impregnation with KOTAB 123, a slow release insecticide. Bed nets

were impregnated following method as described by Schreck and Self. Active ingredient of KOTAB 123 used in permanent net is WHO specified deltamethrin. Detected cases in camp were referred to zonal hospital for further diagnosis and treatment. Interview and observation were held at district and peripheral level health facilities in relation to ACD and case management.
Finding: No of camp attendees: 85; No of fever screened in camp: 53; Fever > 2 weeks: 37; No of rK39 done: 24; rK39 positive: 1; Final diagnosed VL and referred for confirmatory diagnosis and treatment: 1; Skin lesion like PKDL: 0. No of HH in study village: 300; No of bednets in study village: 537; No of bednets impregnated in camp: 536 (99.8%). Vector density per CDC light trap per night before intervention: 14.3; after 2 weeks of intervention: 13.2; after 4 weeks of intervention: 10.7. Cost per combined camp: USD 568.50
Conclusion: It is feasible to combine ACD and vector control with bed net impregnation. ACD for VL/PKDL through combined fever camp should be limited to high endemicity areas. For moderate or low endemicity areas, index and incentive approach of ACD can be applied. For the maintenance phase of the elimination program, rapid surveillance and case detection approach is required.

Year: October 2014 – January 2015
Title: Internal assessment of kala-azar elimination programme of Nepal.
Objective: To review the strategies, programme and implementation at district level as well as collect programme data and information and make recommendation that are program specific for further improvement.
Study design, Sample size: Central level programme managers, district level programme managers, service providers at district, PHCCs, health posts, sub-health posts, physicians treating KA patients, VDC secretaries, FCHVs and community people were interviewed using semi-structured questionnaires. National plan and strategies of Nepal government for VL elimination were reviewed. Epidemiology of KA before and after the elimination initiatives were explored. Data collected were from Morang, Saptari, Mahottari, Sarlahi and Bara for KA programme districts and Okhaldhunga, Palpa and Surkhet for KA non-programme districts.
Finding: Kala-azar national control programme has been operational since 1993 but without much result. Since 2005, under regional KA elimination initiative there has been reinforcement of KA elimination activities. Here after, the number and incidence rate of KA has significantly decreased from 729 cases in 2011 to 575 in 2012 and 325 in 2013 reaching the elimination target at national level. Diagnostic rK39 kit and anti-VL drugs are provided at a free of cost in public health system but there was irregular supply of drugs and diagnostic tool kit at hospital and PHCC. IRS and LLINs coverage is more than 100% in assessed districts however, budget for IRS is inadequate and the surveillance is neglected. New cases are arising from non-endemic areas as well. Patient delay to access KA treatment is still high in both program and non program districts. Behaviour change communication and promotional activities have not been implemented in all KA affected areas.

Conclusion: Nepal is close to KA elimination target. Elimination can be achieved by addressing the weakness on both program and non program districts. Regular supply of diagnostic tool and anti-VL drug is vital along with the strengthening of effective disease surveillance as well as case detection strategies. Awareness raising activities at community level with the involvement of FCHV should be strengthened. Appropriate innovations for behaviour change communication strategies and message designed in local language can improve health seeking behaviour. District level program managers and physicians should be up to date with revised KA control strategy and KA treatment protocol respectively.

Year: 2015-2016

Title: Improved VL case detection and vector control to support the VL elimination initiative in Nepal.

Objective: To determine the most cost-effective and sustainable intervention strategies combining active case detection of VL/PKDL and other fever diseases with vector control at the community level.

Study design, Sample size: 5 program and 5 non-program selected for the study. Detailed review of ACD and vector control strategies was done. Feasibility, cost and result of different strategies of ACD was compared. Approximately 40,000 population per intervention site was screened. For LLINs, randomized control trial was performed in 4 villages with one being control and rest three as interventions. All households from each village were selected for LLINs with KOTAB 123, IRS and wall painting with Inesfly. 6 household from the each cluster were selected for entomology survey at 1, 3, 9 and 12 months in interventions and controls. For cost analysis, combination of bottom-up and top-down approach were applied. Cost efficacy of efficacy of three interventions were compared.

Finding: Total delay from onset of symptoms to reporting: 115 days; Delay was 24 days longer in non-program district. Patient delay in non-program: 31 days and in program: 14 days. Diagnostic delay 73 days in program and 80 days in non-program. Delay to successful therapy: 4 days. Report to central authority: 17 days. Fever >2 weeks in camp: 398 and 1 VL positive among them. 7211 HHs screening for blanket approach, zero VL cases detected. IRS AND KOTAB 123 were highly effective in first month of intervention which gradually decreased after first month. Inesfly paint was effective upto 12 months after intervention. Mortality was 80% for Inesfly paint, 23% for IRS and 26% for KOTAB123.

Conclusion: Compulsory VL notification is suggested. VL program should be expanded into non-program districts and private sectors. Training of the staffs on collecting data, reporting and using electronic media should also be considered. Optimizing and validity of the reports should be present. Early warning and weekly reporting even with zero case is required. Combined camp approach seems feasible and sensitive. Insecticidal wall painting proved to be most effective vector control intervention and therefore can be considered as an alternative or complement to IRS for VL post-elimination program in Nepal.

Year: November 2019
Title: Research support for the consolidation and maintenance phase of the Visceral Leishmaniasis elimination in program in Nepal
Objective: To identify sustainable, cost-effective approaches to find cases and foci of transmission early that are adapted to the consolidation and maintenance phases of the VL elimination programme and can be applied widely and do not require a vertical programme.
Study design, Sample size: After assessing all VL incidence at village level of VL endemic villages, 9 villages based on the stratification of high, moderate and low VL incidence were selected. IRS was performed in 222 households of two villages, IWP in 33 households of one village and 698 bednet impregnation from 242 households of three villages were conducted as a vector control interventions. Final follow-up of ACD through household screening and determination of vector densities were conducted after 16 months of intervention. VL cases from 2013-2017 were analysed from the existing database of EDCCD and District Public Health Office from the plain Terai area. 203 build environment were analysed. Inferential statistics and logistic regression analysis were performed to determine the association of the risk factors with VL. In depth interviews and focus group discussions with FCHVs of 22 VL endemic villages of 3 districts. 203 household heads from same villages were formally interviewed to understand their knowledge, attitude and practice regarding VL.
Finding: Three past VL case and one past tuberculosis case were identified in baseline screening. One past VL and one past leprosy cases were within last 12 months were identified. IRS was not found to be effective in sandflies reduction upto 16 months of interventions whereas IWP and impregnated bednets were found effective. After intervention more than 90% people reported reduction in the sand fly/mosquito densities. The risk factors with the highest odds of VL were in Bamboo walls (8.1), walls made of leaves/branches (2.9) and placing sacks near sleeping areas (19.2). Significant outdoor factors were Kadam trees, open ground-outdoor toilets, moisture in outdoor toilets, nearby- open land, moisture inside animal sheds and surrounding animals/animal waste. FCHVs efficiency based on the family support and incentives. The awareness of VL was based on the peoples' previous exposure to VL and not due to educational programs.
Conclusion: ACD is an important activity of surveillance, which should be continued and cost-effective. ACD of integrated febrile illness should be conducted. IWP and bednet impregnation can be considered for the post attack phase of the elimination program. Awareness on VL should be promoted through FCHVs and other media to foster early case detection and vector control.
Year: October 2019
Title: Early public health response to VL/PKDL cases in low endemic non-program districts of Nepal.

Objective: To study the feasibility, efficacy and cost of ACD (index based approach) and vector control (IRS or wall painting) to respond to new VL case in new VL foci and in low VL endemic areas of Nepal.
Study design, Sample size: Study was conducted in 2 districts i.e Palpa and Surkhet from June 2018 to June 2019. Both quantitative and qualitative research was done to compare the adoption and outcome of two intervention packages with follow up at 1, 6 and 12 months after intervention. First ten VDCs to notify new VL/PKDL cases (index cases) were included in the study. Screening survey for the secondary cases were conducted in 60 houses which was around 100m radius from the houses of index cases. Entomological measurements and household interview survey was held in subsample of these HHs. The IEC activities were covered in the locality.
Finding: 1239 participants in Palpa and 596 participants in Surkhet. 1 VL positive case in Palpa. No PKDL cases. IRS performed HHs: 236. Insecticidal wall painting: 178 HHs. Both IRS and insecticidal paint was well accepted. Sand fly mortality after IRS after one month is 81%, nine months is 59% and twelve months is 63% in comparison to baseline. Sand fly mortality after insecticidal wall painting after one month is 90%, nine months is 81% and twelve months is 75% in comparison to baseline. Cost per HHs for IRS is USD 5.4 and for insecticidal wall painting is USD 17.8.
Conclusion: Consolidation and Maintenance phase of VL elimination program can hugely benefit from ACD, vector control and surveillance. Operational research is needed to identify the transmission mode of the disease in the non-program districts as well as continuous vector surveillance by PHCs.

Annex 7: Visceral leishmaniasis research institutions in Nepal

Institute of Medicine, Tribhuvan University

VL research in Nepal was implemented by the Institute of Medicine, Tribhuvan University, Public Health and Infectious Disease Research Center and BPKIHS. The Institute of Medicine, Tribhuvan University conducted eight implementation research projects in the areas of vector control and treatment during the initial phase of the VL elimination program between 1996 and 2008 supported by WHO/TDR. BP Koirala Institute of Health Sciences, a tertiary care hospital in Dharan, southern Nepal, has implemented four WHO/TDR supported and six other multi-disciplinary VL research projects of various types (randomized controlled trial, vector control, socio-economic and surveillance research) with the support of different funding agencies. The implementation research projects conducted by IOM through WHO/TDR support is presented in Annex 5.

Public Health and Infectious Disease Research Center

Public Health and Infectious Disease Research Center, Kathmandu, Nepal, has conducted 19 WHO/TDR supported research studies in the areas of VL vector control, treatment and surveillance. The projects included capacity building and training of health workers. VL research implemented by PHIDReC through WHO/TDR support is presented in Annex 6.

BP Koirala Institute of Health Sciences (BPKIHS)

BP Koirala Institute of Health Sciences is a tertiary care hospital in Dharan, southern part of Nepal. VL multi-disciplinary research in the area of randomized controlled trial, vector control, socio-economic and surveillance research was carried out with support from different funding agencies. The list of VL projects implemented by BPKIHS, Dharan during the period 2006 to 2019 is as below:

Year	Project	Funder
2016-2019	KalaCore Nepal “Supporting sustainable VL control and elimination in Nepal	UK Government’s DFID
2016-2018	Strengthening Kala-azar Active Case Detection Program in Nepal	PATH Seattle, United States

2014-2016	Kala-azar Focused Pharmacovigilance Program in Nepal	PATH Seattle, United States
2008-2013/ 2014-2016	Framework agreement (FA III): Improving control of neglected tropical disease in Nepal	DGCD and ITM, European Union
2009-2014	KalaDrug-R “Innovative approach to monitor treatment effectiveness”	European Union
2006-2009	KALANET Project “Efficacy, acceptability and cost-effectiveness of long lasting insecticidal nets in the prevention of Kala-azar in Nepal”	European Union

Annex-8: SOP for different active case detection methods

SOP for Different ACD Methods:

To accelerate the elimination program in the district, success of active case detection is important. This approach will help facilitate early detection and prompt treatment. The district health/public health office in coordination with the health institutions from where passive cases are reported should be responsible for planning and implementation of active case detection. The standard protocol for active case detection of KA and PKDL cases is given below:

Index Case Based Approach

Policy/scope: This approach is to be implemented in low KA endemic areas (to be defined in each country) on an ongoing basis throughout the year in communities with newly detected KA cases.

General responsibilities: The District Public/Health Officer is responsible for implementing the activity.

Materials required: 1) Work diary; 2) Patient register; 3) Patient Referral slips; 4) Training manual; 5) Household screening register; 6) Kala azar treatment card; 7) Drug distribution register

Procedures

Preparatory activities at district level

Identify villages where the index case approach will be applied.
Identify and train public health workers / health volunteers in identification and referral of chronic fever cases.
Identify staff at DPHO / DHO responsible for conducting index case search of neighborhood.
Define information sources of index cases—e.g. monthly review meetings at district etc.
Ensure availability of drugs, rk39 test kits, fund requirements, IEC material, treatment cards etc. at the district.
Prepare plan for supervision and M & E of index case-based approach –identify supervision team for supervision activities on a sample basis.
Define reporting system from health facility to district.

Preparatory activities at health post level

Identify and train health workers / health volunteers in identification and referral of chronic fever cases, skin lesion cases (suspected PKDL/CL/MCL).
Identify staff / health volunteers responsible for conducting index case-based search of neighborhood.

Index case-based search activities

Monthly review of all KA cases reported by zonal / district hospital from the district.
List KA patients – name, age, sex and detailed address of patient, name of health post responsible for index case search.
Health post staff visits the community of the index case, traces the home, confirms identity of the patient and alerts the health worker/health volunteer.
Organize house to house search around index case in the same month of reporting of index case using screening forms or format or register.
Screen all individuals for fever ≥ 2 weeks in neighboring households in the village/hamlet around the house of index case done by HP staff and health worker / health volunteer.
Fill patient referral form and refer cases to district / zonal hospital for confirmation of Kala-azar.
Maintain a list of cases referred for confirmation of KA diagnosis.

Inform district / zonal hospital staff of cases referred for KA diagnosis.
Maintain records and report to district on index case finding activities conducted.

Post index case-based search activities at district/zonal hospitals

Ascertain diagnosis of all cases referred by health workers after index case-based search.
Ensure that all Kala-azar cases are started on treatment.
Monitor treatment compliance and side effects.
Ensure timely payment of wage-loss to Kala-azar/PKDL patients.
Ensure timely payment of incentives to Female Community Health Volunteer for case follow-up.
Ensure availability of drugs and diagnostics at hospitals based on number of Kala-azar cases.

Post index case-based search activities at district level

Assess monthly reports on number of Kala-azar cases, drug distribution.
Supply of drugs and diagnostics based on number of Kala-azar cases reported.
Evaluate index case finding activities based on supervision / monitoring reports.

Post index case-based search activities at health post level

1. Inform public health workers of cases diagnosed and started with KA/PKDL treatment to ensure treatment compliance or for any side effects/adverse events.

Camp Approach

Policy/scope: The camp approach is to be implemented in Kala-azar high endemic districts. The camp approach ideally is to be implemented twice a year.

General responsibilities: The District Public/Health Officer is responsible for implementing the camp approach strategies.

Materials required: 1) rK39 kits in a cool box for transport; 2) Lancet & Lancet disposal box; 3) Cotton; 4) Spirit; 5) Gloves; 6) General medicines – anti-pyretics, antibiotics, anti-diarrheal, anti-malarial drugs etc.; 7) Rapid diagnostic kits for malaria (optional in malaria endemic areas) and other diseases, if available; 8) Patient referral form; 9) Lab investigation form; 10) Camp register (Register book); 11) Photo album of PKDL; 12) VL/PKDL patient registration form; 13) IEC materials, banners, posters, pamphlets (local language), pictures of PKDL skin lesions; 14) Mikes; 15) BP apparatus; 16) Thermometer; 17) Stethoscope; 18) Disposable syringes, IV infusion sets etc. (optional); 19) Transport box for drugs, supplies etc.; 20) Emergency drugs – cortisone, anti-histamines, IV fluids, adrenaline; 21) Bio-waste disposal containers; 22) Equipment for starting treatment (optional in areas where treatment will be started in the camp)

Procedures

Pre-camp preparatory activities at district level

List the villages with high Kala-azar incidence (new cases reported).
Conduct a meeting with DP/HO to prepare a micro-action plan at least 1 month before initiation of camps.
Prepare a time schedule for camps—decide number of camps, timings, duration of each camp, list name of villages where camps are to be held etc.
Prepare logistics plan—estimate requirement of drugs, rK39 test kits, lancets, gloves, fund requirements, IEC material etc.
Prepare supervision and monitoring plan for camps—identify supervision team, supervision schedule etc (on a sample basis).
Pre-camp preparatory activities at district level

DPHO/DHO staff meeting to plan camp activities at least 2 weeks before initiation of camps.
 Identify the DPHO/ DHO team (medical officer, nurse, lab technician, health inspector, etc) which will conduct/ coordinate camp activities.
 Define duration of camp (usually one day camp).
 Prepare plan for camp logistics—drugs, diagnostics etc.
 Arrange/provide refreshments for camp team on the day of camp.
 Vehicle requirement.
 Identify and coordinate with village level functionaries/leaders.
 Pre-camp preparatory activities (village level)
 One HP staff (nurse, lab technician, health inspectors or other) conducts coordination meeting at least 1 week before camp with community leaders/members and others to inform and solicit community involvement in publicity and conduct of camp activities.
 Identify venue for camp and determine its suitability for conducting camp.
 Identify, train and assign roles to village functionaries/volunteers / religious leaders/school teachers for camp publicity activities.
 Publicity activities to include miking, public announcement, distribution of pamphlets, putting up of banners/posters in public places, announcement on local FM radio, interpersonal communication by health workers etc.
 Publicity activities to be conducted at least one day prior to camp and on the day of camp.
 List and manage locally camp furniture (tables, chairs, bench, examination table, bedside screens), drinking water provision etc.
 Set up camp one day prior or early morning of the camp day (e.g. Through local volunteers).

Camp day activities

Camp Team: one MO, one lab technician, one nurse, NGO/ community volunteers/school teachers etc.
 Organize flow of camp activities.
 Patient registration (name, address, age and sex).
 Examination of patient for fever ≥ 2 weeks by MO, past history of kala azar, spleen examination, general examination, examination for skin lesions.
 rk39 test to be done by lab technician at camp if fever ≥ 2 weeks and splenomegaly.
 If rk39 test positive, Case Referral form to be filled and given to patient. Case referral register to be completed.
 Kala azar treatment card filled for rk39 positive patients. One copy of treatment card given to patient. Office copy of treatment card archived in district hospital.
 For probable PKDL patients (PKDL-like skin lesions with rk39 test positive and past history of kala azar treatment) will be referred to district/appropriate level hospital for confirmation of diagnosis and treatment start.
 Drug distribution register maintained.
 If rk39 test negative or for all other patients, MO advises appropriate treatment / refers for further diagnostic tests. Particular emphasis may be given to suspected leprosy patients.
 All patients with severe Kala-azar and or other co-infections to be referred to appropriate level hospital.
 Proper disposal of bio-waste at the end of the camp.

Post camp activities at district level

Maintain camp records - camp registers, treatment cards, referral register, drug distribution register.
 Manage patient specific drug box for Kala-azar patients.
 Ensure that patients referred from camp or patients started on KA treatment follow up regularly for further treatment.
 Ensure timely payment of wage-loss monies to Kala-azar patients
 Assessment of camps- Number of attendees, number of chronic fever cases, number of rk39 tests done, number of rk39 test positives, number of patients started treatment for kala azar/PKDL, number of patients referred for KA/PKDL treatment and follow up, drug distribution.
 Assessment of constraints, difficulties of conducting camp.

Submit camp activity reports to district.
Supply of drugs and diagnostics based on number of VL/PKDL cases reported.
Evaluate camp activities based on supervision/monitoring reports.

Post camp activities at village level

1. Inform health workers of patients diagnosed and started with KA/ PKDL treatment to ensure treatment compliance or for any side effects/adverse events.

Note: As PKDL is one of the differential diagnoses of leprosy, all suspected PKDL cases should be ruled out for leprosy. During camp activities health workers who can screen leprosy should be mobilized. Leprosy programme people should be informed of this activity and at district level, district TB and leprosy officer (DTLO) is the appropriate person to coordinate leprosy screening in these camps.

Incentive Based Approach

Policy/scope: The incentive approach is to be implemented in low Kala-azar endemic areas (to be defined in each country) and is implemented on an ongoing basis throughout the year in communities with newly detected Kala-azar/PKDL cases.

General responsibilities: The District Public/Health Officer is responsible for implementing the incentive-based case detection strategies.

Materials required: 1) Work diary; 2) Patient register; 3) Patient Referral slips; 4) Training manual, Pictures of PKDL skin lesions

Procedures:

Preparatory activities at district level

Identify villages where the incentive approach will be applied based on endemicity.
Identify and train health workers / health volunteers in identification and referral of chronic fever cases.
Ensure availability of drugs, rk39 test kits, fund requirements, IEC material, treatment cards etc. at the district.
Prepare plan for supervision and M&E of incentive approach - identify supervision team for supervision activities on a sample basis and based on the report of the cases in the district hospital.
Define reporting system from health post to the DPHO/DHO.
Manage fund for providing incentive.

Preparatory activities at health post level

1. Identify and train health workers/health volunteers in identification and referral of chronic fever cases, skin lesions.

Incentive based search activities

Screen individuals for fever ≥ 2 weeks in the village / hamlet.
Fill patient referral form and refer patients to nearest PHC /district/zonal hospital for confirmation of Kala-azar.
Maintain a list of patients referred for confirmation of KA diagnosis.
Inform PHC/ health post staff of patients referred for KA diagnosis.

Post incentive-based search activities at health post level

Ascertain diagnosis of all patients at the district hospital referred by health workers.

Ensure that all Kala-azar patients are put on treatment.
Monitor treatment compliance and side effects.
Maintain records and report to district about case finding.
Ensure availability of drugs and diagnostics at District Hospital based on number of Kala- azar/ PKDL cases.

Post incentive-based search activities at district level

Assess monthly reports from health facility –Number of kala-azar / PKDL cases, drug distribution.
Supply of drugs and diagnostics based on number of Kala-azar/PKDL cases.
Evaluate incentive-based case search activities based on passively reported cases in the district hospital.

Post incentive-based search activities at health post level

1. Inform health workers/health volunteers about the patients diagnosed and started with Kala- azar/PKDL treatment to ensure treatment compliance or for any side effects/adverse events.

Annex 9: Data Collection Form after the End of the Spraying Cycle at the District Level

Supplies	To be entered	Indicator calculated automatically
#pumps available		%functional pumps available
#functional pumps		
#PPE for how many squads?		% of squads with protective clothing
Insecticide available(tons, kg or sachets)		% quantity of insecticide received that was requested
Insecticide needed/requested (tons, kg or sachets)		
Human resources & training		
#squads hired		%of needed squads actually hired
#squads needed/requested		
#squads trained before start of cycle		%of squads trained before start of cycle
#villages supervised for IRS		%IRS villages supervised
#villages sprayed		
#squads with quality score*		%squads with acceptable quality
#squads observed		
Achievement of targets		
#PHCS targeted for IRS		% of targeted PHCs sprayed
#PHCS sprayed		
#villages with KA in last 3 years ^{\$}		%KA villages targeted for IRS
#villages targeted for IRS		%KA targeted villages sprayed
#Villages sprayed		
#HHs targeted for IRS		%of target HHs sprayed
#HHs sprayed		
HOUSEHOLD SURVEY⁺		
#households interviewed		
#HH who received adequate information		%HH with adequate information
#HH reporting to have been sprayed		%HH covered by IRS
#HH satisfied		%HH satisfied

Annex 10: Sandfly Collection Record Sheet

Name of VDC: _____ Name of village: _____
Name of Cluster: _____

Code: ☐-☐-S ☐ -☐☐

village (1,2,3,4) - collection method (C = CDC Light Trap)-number of the survey (S0, S1,S2, S3) - house number (01-35)
Date: ☐☐/☐☐/☐☐ dd/mm/yy Signature:.....

Sandfly	Males	Females			Total
		Unfed	Fed	Gravid	
<i>P.argentipes</i>					
<i>P.papatasi</i>					
<i>Sergentomyia</i>					

.....
Name of Insect collector

Date:

.....
Entomologist

Annex 11: Bioassay Test Record Sheet

Code the collector:

Code of team leader:

Name of VDC _____

Name of cluster/Village: _____

Name of the insecticide used: _____

Concentration of the insecticide per m²

Test performed in – Lab/ field

Species of the sand fly exposed – *P. argentipes*/ *P. papatasi*

Temperature 24 hour: Max: /Min: /Exposure time:
minutes

Batch Code: --T

Hamlet / VDC (1,2,3,4) - arm-number of the test (T1,T2)

Household Code no.	Surface	Cone No.	Exposure period		24 hours		% Mortality rate	Species of Sand fly exposed	Remarks
			No. Hold	KD	Dead	Alive			
		1							
		2							
		3							
		4							
		5							

Percent control mortality: _____

Percent test mortality: _____

Percent corrected mortality: _____

Signature: _____

Annex 12: Household Screening Register

District: _____	VDC/Municipality: _____	Ward no _____
Village: _____		Date: _____

Name of head of household:Contact Number:

S N	Name	Contact Number (if)	Age (years)	Sex (1=ma le, 2=fem ale)	Suffered from KA during past 1 year or presently		Curre ntly with fever ≥ 2wee ks (1=ye s, 2=no)	Skin lesio n like PKD L (1=y es 2=no)	Examination of suspected VL patient	
					(1=ye s, 2=no)	If yes, date of diagnos is (mm/yy yy)			Spleen enlarge d (1=yes; 2=no; 9=not done)	rK39 test result (1=pos; 2=neg; 9=not done)
1										
2										
3										
4										
5										

Name of health worker: _____

Date: _____

Annex 13: Camp Attendance Register

District: _____	VDC/Municipality: _____	Village: _____
Date: _____		

SN	Name	Ward	Village	Contact Number (if)	Age (years)	Sex (1=male , 2=female)	Suffered from KA in the past / currently		Currentl y with fever > 2weeks (1=yes, 2=no)	Skin lesion like PKDL (1=yes 2=no)	Examination of probable VL patient	
							(1=yes, 2=no)	If yes, date of diagnosis (mm/yyyy)			Spleen enlarged (1=yes; 2=no; 9=not done)	rK39 test result (1=pos; 2=neg; 9=not done)

Annex 14: Case referral form

Only for the patient with fever+splenomegaly+rk39 positive OR patient with past history of KA+Skin lesion+rk39 positive)

Referred from: 1=camp; 2=house to house search; 3=incentive approach

- Name of patient: _____
- Name of head of household: _____
- District: _____ VDC/Municipality: _____ Ward# _____ Village: _____
- House hold No:..... (to be copied from HH screening form)
- Patient ID: ____ (recorded as 001,002,..)
- Patient Age (in years): / ____ / (record as 0 if less than 1-year age)
- Patient Sex: / ____ / (1-male, 2-female)
- Date: _____

- Splenomegaly: 1= yes / no / not examined
- rk39 test result: positive / negative / not done
- Suspected case of VL? Yes / no
- Suspected case of PKDL? Yes / no
- Referred to: (name of doctor/hospital/ PHC)
- Reason for referral: For confirmation of suspected diagnosis of VL/PKDL
 - For rk39 test
 - For treatment
 - Any other reason _____

Name of referring doctor/health worker/FRA: _____

Signature: _____

Date: _____

► one copy to be retained by referring health worker

Annex 15: Patient treatment card

District: _____

Health facility name: _____

Health facility code: _____

Unique patient ID code: NPL-VL-____ - 20__ - ____ Date of admission: _____ (DD/MM/YYYY)

Registration number: _____

Patient's Name: _____ Sex: ☐ Female ☐ Male Age: _____ (years)
Caste: Dalit/Janjati/Madheshi/Muslim/Brahman/Chhetri/others; Patient contact no: _____
Father/Husband's/family head's name: _____

Address:

Household Identification: _____ Village: _____ Ward no: _____
VDC/Municipality: Metropolitan city/sub-metropolitan city/rural municipality/ urban municipality
District: _____ Province: _____ Country: _____

Patient's Information:

Date of onset of symptoms: _____

Time elapsed between onset of symptoms and admission, in days: ____

Does the patient live or work in a VL endemic area ☐ Yes ☐ No ☐ Unknown .

Has the patient travelled to VL endemic areas in last 2 years ☐ Yes ☐ No ☐ Unknown

Probable place of infection: ☐ Same as place of residence ☐ Same as place of residence

Country: _____ **Province :** _____

District: _____ **Ward:** _____ **Village/town:** _____

Infection acquired outside the country : imported case ☐ Yes ☐ No ☐ Unknown

Source of detection: active case detection/passive case detection

Laboratory examination

Rapid diagnostic test : ☐ Yes ☐ No

Date of test (dd/mm/yyyy) ____/____/____ Result ☐ positive/☐ neg/☐ inconclusive/ ☐ unknown

DAT: ☐ Yes ☐ No

Date of test (dd/mm/yyyy) ____/____/____ Result ☐ positive/☐ neg/☐ Borderline/ ☐ unknown

Microscopy (Spleen/BM/Lymph node aspirate): ☐ Yes/☐ No

Date of test (dd/mm/yyyy) ____/____/____ Result ☐ positive/☐ negative/☐ inconclusive/ ☐ unknown

How was the VL case confirmed: ☐ RDT ☐ DAT ☐ Parasitology ☐ Clinically Only ☐ Unknown

Name of the diagnostic centre (if diagnosis was made in other centre): _____

Diagnosis: 1. Primary KA 2. Relapse-KA 3. PKDL 4. CL/MCL

Pregnant: Yes/No **Breast feeding:** Yes/No

HIV status: Reactive/Non-reactive/Not done (unknown)

Any other disease diagnosed: _____

Date of treatment started: _____ Treatment end date: _____

Treatment given:

☐ **No treatment given**

☐ Liposomal Amphotericine B (AmBisome®)

Dosage _____

☐ Liposomal Amphotericine B (AmBisome®)+ Paromomycin

Dosage _____

☐ Liposomal Amphotericine B (AmBisome®) + Miltefosine

Dosage _____

☐ Amphotericin B deoxycholate

Dosage _____

☐ Miltefosine

Dosage _____

☐ Other (specify _____)

Dosage _____

☐ Unknown

Was the treatment completed?

☐ Yes

☐ No

If No, give reason(s):

☐ No, **Stopped for medical reason**

☐ No, **Defaulter**

☐ Unknown

Signature of MO:

Name:Date:

Seal of the health institution:

Patient's follow up**Initial Treatment Outcome (between 1, 2 to 4 weeks following initial treatment start)**

Date of initial follow-up appointment ____/____/____

Clinical Assessment _____

Initial Outcome:☐ Initial cure☐ Failure/non-response☐ Death : specify the cause of death:☐ Death due to VL☐ Death due to HIV☐ Death due to other disease☐ Death due to SAE (Iatrogenic)☐ Death due to non-medical condition (accident)☐ Death due to unknown cause☐ Referred☐ Unknown/Lost-to-follow-up**Final Treatment Outcome (6 months after treatment completed)**

Date of final follow-up appointment: ____/____/____

Clinical Assessment _____

Laboratory test _____

Result ☐ positive/☐ neg/☐ inconclusive/ ☐ not done**Final Outcome:**☐ Final cure☐ Relapse☐ Death :☐ Death due to VL☐ Death due to HIV☐ Death due to other disease☐ Death due to SAE (Iatrogenic)☐ Death due to non-medical condition (accident)☐ Death due to unknown cause☐ Unknown/Lost-to-follow-up

Examination and laboratory findings before and after treatment

Date of Visit (Before Treatment)	Date of Visit (after Treatment):
Temp: °F	Temp: °F
Weight: kg	Weight: kg
Pulse: /min	Pulse: /min
BP:	BP:
Spleen size:	Spleen size:
Hb%:	Hb%:
Creatinine:	
Malaria parasite:	
ALT (SGPT)	
AST (SGOT)	
Potassium (K ⁺)	

Treatment
☐ No treatment given

Date of administration: Duration of treatment: Treatment Given at- daily/ alternative day				Dose of the drug: Date of 1st treatment received: (in case of relapse)			
Drug received	Batch No/expiry date	Drug dose & unit	Frequency	Route	Start Date	End Date	Was drug stopped for ADR (Yes/no)
L-AmB							
L-AmB+ Miltefosine							
L-AmB+ Paromomycin							
Amphotericin B deoxycholate							
Miltefosine							
Paromomycin							
Other.....							

Concomitant drugs							
Name	Indications	Batch No/expiry date	Drug dose & unit (if I.V) infusion rate in ml/hour	Frequency	Route	Start Date	Stop Date

Adverse event information

Reporter's Narrative: (describe the course of events, timing and suspected causes):			
Adverse event/reaction term	Event 1	Event II	Event III
Date of onset	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY
Date of resolved	DD/MM/YYYY	DD/MM/YYYY	DD/MM/YYYY
Severity	Mild Moderate Severe	Mild Moderate Severe	Mild Moderate Severe
Seriousness	Non-serious ADR Serious ADR Please specify category: ☐ Death ☐ Hospitalization/prolonged ☐ Life threatening ☐ Permanent disability/disabling ☐ Congenital anomaly/birth defect ☐ Other medically important condition	Non-serious ADR Serious ADR Please specify category: ☐ Death ☐ Hospitalization/prolonged ☐ Life threatening ☐ Permanent disability/disabling ☐ Congenital anomaly/birth defect ☐ Other medically important condition	Non-serious ADR Serious ADR Please specify category: ☐ Death ☐ Hospitalization/prolonged ☐ Life threatening ☐ Permanent disability/disabling ☐ Congenital anomaly/birth defect ☐ Other medically important condition